Can Building a Community of Practice Improve Pharmacovigilance in Low-Resource Settings?



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For Albert Degg, Grandad

A man who inspired a lifetime of tenacity and curiosity

Abstract

Undertaking effective drug safety monitoring can be particularly challenging in Low-Resource Settings (LRSs) due to a lack of infrastructure, weak regulatory systems and poor access to training and education. Having identified that more could be done to provide or draw together existing free or low-cost resources, Global Pharmacovigilance (GPV), an online platform dedicated to pharmacovigilance activities in LRSs was launched on The Global Health Network (TGHN) in mid-2016.

This action research project sought to investigate whether GPV's membership could be harnessed to work together in a Community of Practice (CoP) on specific challenges facing pharmacovigilance in LRSs, and to assess the impact of the CoP outcomes on the work of those engaged in pharmacovigilance activities in LRSs. Participants were invited to work together to develop relevant training, guidance, tools and/or resources to address the challenges identified, using the online environment as the workspace for discussions, networking and dissemination of outputs.

Following the emergence of the COVID-19 pandemic during the course of this research, and given its significant impact upon health systems globally, it was deemed essential to ensure that pharmacovigilance stakeholders in LRSs had the capacity to address both the exacerbated pre-existing and novel challenges that they were facing. The focus of the research was accordingly contextualised to focus on the greatest challenges facing pharmacovigilance in LRSs during the COVID-19 pandemic.

Adopting an action research mixed methods approach, this project built upon on a rapid consensus-gathering methodology developed by TGHN, which had been implemented successfully to address wider COVID-19 research priorities and iteratively drive the improvement of knowledge, skills and methods gaps in the field of Global Health.

This began with a novel, hybrid knowledge synthesis strategy to identify published literature and existing training and education resources relevant to pharmacovigilance in LRSs. Consensus-gathering activities began with an online survey of GPV members, to identify highly-ranked areas for pharmacovigilance improvement in LRSs during the pandemic. Survey development included the implementation and assessment of a novel, hybrid validity testing methodology. A virtual open workshop was then hosted to share the survey findings with the CoP, invite further discussion on the results, and to reach consensus on the highest priorities at that time. Two international virtual working groups were then formed, each focussing on one of the highest priorities identified in the consensus-gathering activities. These working group were supported by GPV to work together to facilitate the development of (or provision of, if already available elsewhere) pharmacovigilance resources to address the priorities identified.

A significant number of challenges to the conduct of pharmacovigilance in LRSs were identified. The highest priorities for pharmacovigilance in LRSs during the COVID-19 pandemic included ensuring the safe use of medical interventions in vulnerable populations (particularly children and pregnant women), improving communication between pharmacovigilance stakeholders, and increasing local agency of local pharmacovigilance data.

The CoP model represented an effective strategy for fostering collaboration and enabling knowledge exchange and generation amongst pharmacovigilance stakeholders in LRSs. In addition, the CoP approach facilitated the successful identification of the highest priorities for pharmacovigilance in LRSs during the COVID-19 pandemic, where tools, education and guidance

were needed. Whilst the implementation and impact of resources to address these challenges was not assessed, the CoP model was shown to provide an effective platform for the collaborative, community-led development of such resources through the conception of clear and ambitious intervention proposals by highly-engaged working group members.

A knowledge community approach was found to offers an effective strategy for guiding improvements to pharmacovigilance activities in LRSs. The democratic, participant-led methodology provides direct solutions to many of the challenges facing pharmacovigilance in these regions, through the creation of inter-organisational and international networks, the holistic approach to participant contribution, and the collaborative approach to resource sharing and development. The adoption of a knowledge community approach either as the core element of pharmacovigilance capacity building initiatives, or as supporting element to guide such initiatives, has the potential to greatly improve pharmacovigilance capacity in LRSs, and reduce the inequities amongst pharmacovigilance stakeholders around the globe.

Statement on the Impact of the COVID-19 Pandemic upon this Research

The below information has been compiled in accordance with the University of Oxford Medical Sciences Division document '*Documenting impact of Covid-19 on PGR study at assessment stages and in the final examination*'.

i) Background and Research Prior to the Closure of University Buildings

This research began following my matriculation at the University of Oxford in October 2018. The first cases of COVID-19 were reported to the World Health Organisation on 31st December 2019. Following the subsequent emergence of a global pandemic, the University closed its public spaces and issued work-from-home guidance to all staff and students in March 2020, in line with government guidance.

This shift occurred approximately one year and five months after the commencement of my DPhil, following the completion of my transfer to DPhil status in December 2019. The work-from-home guidance remained largely in place (notwithstanding intermittent lifting and reimplementation) until February 2022, at which point hybrid at-home/onsite working routines were recommended by my department. My confirmation of status was conducted remotely in October 2021.

Prior to the closure of University buildings, the title of my research project was 'Can Building a Community of Practice Improve Pharmacovigilance in Africa?', the geographic focus a result of Africa having been identified as a region of particularly low pharmacovigilance capacity following my literature search. As outlined in my transfer of status, I planned to invite the membership of an online pharmacovigilance community of practice to engage in consensus-building activities, (involving a survey, in-depth interviews and focus group discussions), in order to identify the immediate priorities for pharmacovigilance in Africa at that time, and to then invite the community members to work together to develop solutions to address the priorities identified. At the time of closure of the University buildings, I had completed the knowledge synthesis phase of my research (literature and scoping review) and was in the process of designing my initial consensus-building survey.

ii) Detailed Plans/Protocols for Intended Studies

Not applicable

iii) Details from Student's COVID-19 log

The COVID-19 pandemic resulted in the following changes of my personal and professional circumstances:

- Shift from onsite working to working from home, for a period of approximately two years (drastically reducing opportunities for face-to-face contact and discussion with my supervisors, supportive colleagues and my DPhil peers).
- Restriction of my working environment to the home, which for a significant period of time (approximately a year and a half) confined my work environment to my bedroom.
- A forced need to adapt my proposed methodology (face-to-face in-depth interviews and focus group discussions) to remote (virtual) activities (see below).
- Change of research project title, from 'Can Building a Community of Practice Improve Pharmacovigilance in Africa?' to 'Can Building a Community of Practice Improve Pharmacovigilance in Low-Resource Settings?' to reflect the global impact of the COVID-19

pandemic, and focus my consensus building activities to the immediate knowledge gaps surrounding the safety of novel COVID-19 vaccines and therapeutics.

- Considerable additional workload, and subsequent reduction in time available to conduct my DPhil research, due to the establishment and coordination of the COVID-19 (then 'Coronavirus') Research Implementation and Knowledge Hub (see below), for a period of approximately 1 year (January-December 2020).

iv) COVID-19 Related Research

In tandem to my DPhil research, from January 2020 I led The Global Health Network's (TGHN) rapid response to the emergence of COVID-19. This involved the establishment and coordination of the COVID-19 (then 'Coronavirus') Research Implementation and Knowledge Hub, a novel TGHN member hub and community of practice, designed to meet the immediate demand for support and guidance for researchers in Low Resource Settings (LRSs) as the pandemic unfolded. Given the enormous global burden of the then snowballing pandemic upon health systems and populations globally, I considered this work to be a high scientific, professional and moral priority.

This work included:

- The establishment, development and continual maintenance of the online platform, including the identification and production of relevant content (a significant task given the rapid pace and development of new knowledge in relation to the COVID-19 pandemic), digital design and curation of the online space, and fostering the evolution of the Knowledge Hub's online community of practice.
- The refinement and implementation of a rapid, efficient, crowdsourcing consensus-building methodology, involving the use of surveys, online workshops and working groups, to enable the immediate identification of research priorities and knowledge gaps in relation to COVID-19 research in LRSs during the early stages of the pandemic. This methodological framework was then adopted as a core element of my own DPhil project
- Through the arrangement and conduction of virtual meetings, establishing professional connections with relevant collaborates to build the COVID Hub network, expand the CoP and conduct collaborative consensus-building research.
- The coordination of two working groups (focussed on COVID-19 vaccines and COVID-19 diagnostics), including the curation of dedicated digital spaces for both groups, the arrangement of regular groups meetings and communications, and supporting the development of group outputs, namely outlines for two position papers. This provided invaluable experience in working group establishment and co-ordination which I was later able to harness in my DPhil research.

As the pandemic progressed, the development of novel COVID-19 vaccines and therapeutics from December 2020 onwards presented an opportunity for my DPhil research. I elected to pivot the scope and title of my project from 'Can Building a Community of Practice Improve Pharmacovigilance in Africa?' to 'Can Building a Community of Practice Improve Pharmacovigilance in Low-Resource Settings?' to reflect the global impact of the COVID-19 pandemic, and focus my consensus building activities to the immediate knowledge gaps surrounding the safety of the novel vaccines and therapeutics in LRSs globally.

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A DPhil or PhD is no small undertaking, no matter what you call it. This research would have been impossible were it not for the invaluable support of colleagues, friends and family from around the globe. To everyone that has supported these endeavours over the past four years, I offer my utmost gratitude.

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Statement on the Attribution of Work Performed

All activities conducted under the supervision and guidance of Professor Trudie Lang (University of Oxford) and Dr Elizabeth Allen (University of Cape Town).

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Knowledge Synthesis

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Execution, analysis and write-up	R. Walker

Scoping Review

Search strategy design	R. Walker (guidance on use of search software provided by G. Hajduk)
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Survey distribution, promotion and communications	R. Walker, supported by Z. Al-Rawni
Analysis and write-up	R. Walker

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Taking and dissemination of working group meeting minutes	R. Walker
Curation of working group mailing lists	R. Walker
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Analysis and write-up	R. Walker

Coordination of the Global Pharmacovigilance Platform

Identification, upload, and curation of relevant information and resources	R. Walker, E. Allen
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COVID Hub

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- Identification, upload, and curation of relevant information and materials to be shared
- Creation of written content
- Webpage design
- Workshop and webinar scheduling, chairing and digital support
- Working group co-ordination (R. Walker's specific contributions involved the coordination of two online working groups)
- Chairing of working group meetings
- Production of reports on working group activities

Supporting the development of working group outputs (R. Walker's specific contributions involved facilitating the development of two position paper outlines).

Table of Contents

List of Figures 14
List of Tables 16
List of Abbreviations 17
Structure of this Thesis 21

Part I: Introduction, Methodological Background and Research Question 23
I Introduction 25
1 Chapter Overview 25
2 Pharmacovigilance 25
3 Contextualising Global Health Research 30
4 Communities of Practice 34
5 Aims of this Thesis 41
II Knowledge Synthesis 43
6 Rationale 43
7 Methods 43
8 Results 47
9 Conclusion 64
10 The COVID-19 Pandemic: Adapting to Circumstance 65

Part II: Methods 69
III Study Design 71
11 Theoretical Approaches 71
12 Research Platforms 78
13 Contextualisation 78
14 Population of Interest and Participant Recruitment 80
15 Ethical Approval 80
16 Overview of Methodological Components 81
17 Consensus Building Methods: Survey Validation 83
18 Consensus Building Methods: Survey 102
19 Consensus Building Methods: Workshop 104
20 Implementation Methods: Working Groups 113
21 Coordinating the Global Pharmacovigilance Platform 119
22 Timeline Overview 120

Part III: Consensus Building Results 121
IV Survey Validation 123
23 Survey Objectives 124
24 Results 124
25 Discussion 133
26 Conclusion 147
V Survey Implementation 149
27 Results 149
28 Discussion 159
29 Conclusion 175
VI Workshop 177
30 Workshop Objectives 177
31 Results 179
32 Discussion 185
33 Conclusion 207

Part IV: Implementation 209
VII Working Groups 211
34 Working Group Objectives 211
35 Results 212
36 Outcomes to Date 223
VIII GPV Platform 229
37 Results 229
38 Discussion 232

Part V: Discussion 237
IX General Discussion 239
39 Context-Relevant Research 239
40 Engaging all Stakeholders 243
41 Pharmacovigilance in LRSs 245
42 Rapid Democratic Consensus Building 247
43 The Knowledge Community Approach to Capacity Building 249
44 Sustainability 255
X Conclusions 257
XI Limitations 260

Part VI: Bibliography and Appendices 263
XII Bibliography 265
XIII Appendices 275

List of Figures

Figure 1: The structural elements of a CoP, as proposed by Wenger et al. 36
Figure 2: Constituent elements of this research within the CoP model 40
Figure 3: An economic (A) and 'alternative capacity' (B) comparison of WHO PIDM full member countries over time 49
Figure 4: Types of resource identified during the scoping review 57
Figure 5: Institutions that developed resources identified in the scoping review (n) 58
Figure 6: Triangulation vs Embedded mixed methods design 72
Figure 7: Adaptive Embedded Design Framework 72
Figure 8: The 'Action Research' or 'Lewinian' Spiral 74
Figure 9: Levels of CoP participation 77
Figure 10: The stages of this research within the action research spiral 82
Figure 11: Validation Questionnaire Validity Scale 98
Figure 12: Graphic used to promote the survey across social media and TGHN 104
Figure 13: Graphic used to promote the workshop across social media and TGHN 109
Figure 14: Question 2 of the working group registration form 115
Figure 15: Question 2 of the working group registration form with positive option selected 115
Figure 16: Timeline of major methodological milestones 120
Figure 17: Survey validation methodology within the action research cycle 123
Figure 18: Regions represented by questionnaire validation content experts 125
Figure 19: Recommendations for additional knowledge gap questions in the questionnaire 127
Figure 20: Qualitative feedback on questionnaire design 128
Figure 21: Example knowledge gap question structure 139
Figure 22: Survey methodology within the action research cycle 150
Figure 23: Countries represented by survey respondents 151
Figure 24: Job roles (A) and institutions (B) of survey respondents 152
Figure 25: What does the term 'pharmacovigilance' mean to survey respondents? 153
Figure 26: The relevance of pharmacovigilance to pharmacovigilance stakeholders in LRSs 154
Figure 27: The ten highest-ranked 'pharmacovigilance in LRSs during the COVID-19 Pandemic' themes to which survey participants agreed that they 'needed to know more about' 155
Figure 28: Overview of themes identified from free-text responses to the question 'What other areas of general vaccine PV are you interested in?' 156

Figure 29: Overview of themes identified from free-text responses to the question ‘What other areas of COVID-19 vaccine PV are you interested in?’ 157
Figure 30: Overview of themes identified from free-text responses to the question 'What other patient groups are you interested in?' 157
Figure 31: Overview of themes identified from free-text responses to the question 'What other areas of COVID-19 medicine PV are you interested in?' 158
Figure 32: Overview of themes identified from free-text responses to the question 'What else would you like to know about PV systems and communications during the pandemic?' 158
Figure 33: Pharmacovigilance themes represented in the 10 highest ranked pharmacovigilance items. The area of each sphere is proportional to that theme’s frequency in the top 10 167
Figure 34: Overview of themes relating to pharmacovigilance in LRSs that emerged from free-text responses to all knowledge gap questions. 169
Figure 35: Workshop methodology within the action research cycle 178
Figure 36: Countries represented by (A) workshop attendees and (B) poll participants 180
Figure 37: Job roles (A) and institutions (B) of workshop attendees and poll respondents 181
Figure 38: Did workshop participants feel that the 10 highest pharmacovigilance priorities identified in the survey remained relevant to their setting at the time of the workshop? .. 183
Figure 39: Themes relating to pharmacovigilance in LRSs that emerged during the workshop ... 195
Figure 40: Working Group methodology within the action research cycle 212
Figure 41: Collective membership registrations of both working groups, Mar-Aug 2022 214
Figure 42: Countries represented by (A) Children and Pregnancy Working Group members and (B) Data Analysis Working Group members 215
Figure 43: Job roles (A) and institutions (B) of working group members 216
Figure 44: Pharmacovigilance experience of working group members 217
Figure 45: Working group attendance Apr-Aug 2022 218
Figure 46: Screenshots from the working group webpages on GPV, Aug 2022 222
Figure 47: GPV membership over time 230
Figure 48: The 10 countries with the highest number of GPV sessions. (A) All countries and (B) LMICs only 231
Figure 49: Examples of webpages developed on GPV 2018-2022 233
Figure 50: Evolution of the Pharmacovigilance CoP 250
Figure 51: Porous (A) and Nebulous (B) visualisations of a CoP 251

List of Tables

Table 1: A comparison of learning theories, their associated paradigms, and metaphors of learning 35
Table 2: List of trial keywords used to guide final search strategy 45
Table 3: List of 18 search terms used to refine the search strateg 46
Table 4: List of keywords used during the scoping exercise 46
Table 5: Resource Scoping Review Search Results Breakdown 57
Table 6: Relevant educational resources or learning materials returned for each search term used in the three-level search 59
Table 7: An overview of the four main types of validity 87
Table 8: Survey validation debriefing discussion outcomes 129
Table 9: Challenges facing pharmacovigilance in LRSs raised by survey validators 130
Table 10: Questionnaire CVI scores at all stages of testing 132
Table 11: Items included in the first round of content validity testing that scored an acceptable I-CVI but were amended or removed from the questionnaire 136
Table 12: Ranking of pharmacovigilance priorities in LRSs during the COVID-19 pandemic 182
Table 13: Themes, codes and sub-codes that emerged in the open workshop 184
Table 14: LMIC involvement and the top five countries represented by participants across all research activities 240
Table 15: Comparison of three metaphors of learning 253
Table 16: Example distinctions between CoPs and IKCs 254

List of Abbreviations

AAS	African Academy of Sciences
ACP	Average Congruency Percentage
ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
AMRH	African Medicines Regulatory Harmonization
BST	British Summer Time
CDC	Centres for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
CoP	Community of Practice
COVID-19	Coronavirus Disease 2019
COVID Hub	COVID-19 Research Implementation and Knowledge Hub
CVI	Content Validity Index
DAC	Development Assistance Committee
DCVMN	Developing Countries Vaccines Manufacturers Network
DEG	Diethylene Glycol
DSRU	Drug Safety Research Unit
EC	Executive Committee
EEC	European Economic Community
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUCROF	European Contract Research Organisation Foundation
EUL	Emergency Use Listing
FDA	Food and Drugs Administration
Fig.	Figure
G7	Group of 7
G77	Group of 77
G8	Group of 8

GACVS	Global Advisory Committee on Vaccine Safety
GMT	Greenwich Mean Time
GNI	Gross National Income
GPV	Global Pharmacovigilance
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
HIC	High Income Country
HRS	High Resource Setting
ICSR	Individual Case Safety Report
I-CVI	Item-level Content Validity Indices
IKC	Innovative Knowledge Community
IP	Internet Protocol
ISoP	International Society of Pharmacovigilance
ISPE	International Society for Pharmacoepidemiology
LDC	Least Developed Country
LMIC	Low and Middle-Income Country
LRS	Low-Resource Settings
MHRA	Medicines and Healthcare products Regulatory Agency
MSH	Management Sciences for Health
NMRA	National Medicines Regulatory Authority
NSAID	Non-Steroidal Anti-Inflammatory Drug
ODA	Official Development Assistance
OECD	Organisation for Economic Co-operation and Development
PAR	Participatory Action Research
PAVIA	PhArmaco Vigilance Africa
PIDM	Programme for International Drug Monitoring
PROFORMA	Pharmacovigilance Infrastructure and Post-Marketing Surveillance System Capacity Building for Regional Medicine Regulatory Harmonization in East Africa.
PV	Pharmacovigilance
PViMS	PharmacoVigilance Monitoring System
Q&A	Question and Answer
RIG	Regional Interest Group

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
S-CVI	Scale-level Content Validity Indices
S-CVI/Ave	Scale-level Content Validity Indices/Average
S-CVI/UA	Scale-level Content Validity Indices/Universal Agreement
SF	Substandard and Falsified (medicinal products)
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
SIDS	Small Island Developing State
SIG	Special Interest Group
TAF	Total Agreement Frequency
TGHN	The Global Health Network
UK	United Kingdom
UMC	Uppsala Monitoring Centre
UN	United Nations
UN-OHRLLS	United Nations Office of the High Representative for the Least Developed Countries, Landlocked Developing Countries and Small Island Developing States
US	United States (of America)
UTC	Coordinated Universal Time
VPN	Virtual Private Network
WHO	World Health Organisation
WHO-AFRO	World Health Organisation Regional Office for Africa

Structure of this Thesis

This thesis is organised into six parts:

- **Introduction, Methodological Background and Research Question**: Chapter I will provide a background to this research, and overview of the each of the component elements, and outline the research aims. Chapter II will present a novel hybrid knowledge synthesis strategy.
- **Methods**: Chapter III will discuss the theoretical methodological concepts that underpin the study design, and provide and in-depth overview of the specific methods undertaken at each stage of this research
- **Consensus Building Results**: Chapters IV, V and VI will present the findings of a crowd-based consensus-building approach to the identification of research priorities, namely a novel research-tool validation process, a cross-sectional survey, and an online open workshop.
- **Implementation Results**: Chapter VII will discuss the establishment of two international working groups to address the priorities identified in Part III, and their activities to date. Chapter VIII will present an overview of the uptake and usage of an online pharmacovigilance platform.
- **General Discussion**: Chapter IX will present a collective summarising of each of the stages of this research in relation to the research aims. Overall conclusions and limitations are presented in Chapters X and XI.
- **Bibliography and Appendices**: Chapters XII and XII contains the bibliography of referenced literature and supporting materials.

Part I: Introduction, Methodological Background and Research Question

I Introduction

1 Chapter Overview

This thesis seeks to assess whether a Community of Practice (CoP) approach can improve pharmacovigilance in Low-Resource Settings (LRSs). In this Chapter, I will introduce each of the core elements of this research question, namely pharmacovigilance, LRSs and CoPs, and outline the formation of the research question.

2 Pharmacovigilance

The World Health Organisation (WHO) defines pharmacovigilance as:

> '*The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem'* [1].

Pharmacovigilance is a multifaceted field and its scope has gradually expanded from a focus on conventional medicines over recent decades. Its concerns are currently agreed to include the safety surveillance of traditional, complementary and herbal medicines, blood products (haemovigilance), vaccines, biologicals and medical devices (materiovigilance). In addition to encompassing this gamut of medicinal products, pharmacovigilance also concerns medicine interactions, medication errors, substandard and falsified medicines, and the abuse and misuse of medicines. Drug safety surveillance activities occur at all stages of a product's life cycle, from the preclinical to the post authorisation phases [2-4]. Most recently, the pharmacovigilance sector has been identified as a key stakeholder in other fields of public health, including Antimicrobial Resistance and One Health [5, 6]. Fundamentally, pharmacovigilance aims to limit harm to patients and promote the safe and effective use of medicines.

2.1 A Brief History of Pharmacovigilance

The science of pharmacovigilance is a modern one, its rapid development fuelled largely by events in the 20th century. Nevertheless, examples of an awareness of the risks posed by medical interventions can be found across the ancient world [4]. Indeed, in the field of medicine, an omnipresent reminder of the dichotomous relationship between the benefits and harms of medical treatment is found in the prefix 'pharma-', derived from the ancient Greek 'Pharmakon', meaning both 'Remedy' and 'Poison' [7].

Evidence of scattered efforts at medicines regulation around the globe over the following millennia is sparse. Public interest in the safe use of medicines began to expand rapidly in the 1800s, driven by the rapid industrialisation of the pharmaceutical sector, an increase in the availability of medicines, and a series of tragedies and scandals [4].

Whilst there had been previous advancement of medicines regulation in the United States of America (US, see also **8.1**), the thalidomide tragedy of the 1950s-60s is commonly described as the flashpoint of modern pharmacovigilance. Between 1956-63 the drug was produced and marketed under license across Europe, Australia and Japan* as a hypnotic and antiemetic, and was widely prescribed and sold over-the-counter for a range of conditions, including pneumonia, the common cold, influenza and morning sickness [4, 8]. Thalidomide was promoted as being 'free of side effects', and was prized as a sedative for its lack of 'morning hangover' effect [9]. It was later to emerge that thalidomide had undergone limited preclinical investigation, especially regarding toxicity studies, and was never tested in pregnant animals before its use in humans [10].

*Thalidomide was not approved for use in the US, primarily thanks to the work of Dr Frances Kelsey of the US FDA (Food and Drug Administration), whose repeated requests for further toxicity data delayed FDA approval until international evidence of the teratogenic effects of thalidomide surfaced. Nevertheless, incidences of thalidomide deformity did occur in the US (albeit on a much smaller scale than in Europe), primarily as a result of 'free samples' of thalidomide provided to doctors by the manufacturers.

By 1961, reports of the severe birth defect phocomelia* (a condition involving malformations of the arms and legs, literally meaning 'seal limbs'), surfaced in newborns whose mothers had taken thalidomide during the first trimester of pregnancy [9, 11, 12]. In response to these reports, thalidomide was withdrawn from the market in West Germany and the United Kingdom (UK) in 1961, and withdrawals continued across other countries between 1961-1963. The rapid drop in incidence of congenital malformations following thalidomide's withdrawal all but confirmed its role as the causative agent. In the years following thalidomide's withdrawal, an abundance of evidence demonstrating the teratogenic and embryopathic effects of the drug in animals was published in the medical literature [10].

In total, an estimated that 10,000 children worldwide suffered congenital malformations as a result of *in utero* thalidomide exposure between 1956 and 1962, many not surviving more than a few days beyond birth [13].

In response to the catastrophe, a wide range of regulatory actions were taken, including the Kefauver-Harris Amendments 1962 (US), requiring the safety and efficacy of drugs to be demonstrated prior to approval, the Medicines Act 1968 (UK) which provided the UK's first centralised, structured pharmaceutical regulation and led to the establishment of a statutory medicines licensing authority (which was to eventually become the Medicines and Healthcare products Regulatory Agency, MHRA), and the first European pharmaceutical directive (65/65/EEC, 1965). The UK's 'Yellow Card' AE voluntary reporting form was developed in 1964, whilst drug safety surveillance systems were established in Norway and Sweden in 1965, and Japan in 1967 [4, 7, 14, 15].

The 1960s also saw the establishment of the WHO Programme for International Drug Monitoring (PIDM, 1968), following the 16th World Health Assembly. Founded by 10 member countries, the

*Prior to reports of phocomelia, initial reports of peripheral neuropathy in adults treated with thalidomide surfaced as early as 1960. These reports contributed to Kelsey's reluctance to approve thalidomide in the US.

programme supports the international collection and assessment of ICSRs (Individual Case Safety Report), and has been managed by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) since 1978 [4]. As of 2022 the PIDM has 153 full member countries and 22 'Associate Members' (considered to be in the early stages of establishing their pharmacovigilance systems, having not yet fulfilled the requirements for full membership) worldwide.

The enormous increase in medicines regulation following the thalidomide tragedy led to an associated increase in the identification of medicines safety issues. Examples include the cases of Practolol (selective beta-blocker, withdrawn in the UK, 1976, following reports of oculomucocutaneous syndrome and sclerosing peritonitis), Benoxaprofen (NSAID, withdrawn in the UK, Europe and the US, 1982, following reports of photosensitivity and serious hepatotoxicity), Cervistatin (statin, withdrawn worldwide, 2001, following reports of rhabdomyolysis) and Rofecoxib (NSAID, withdrawn worldwide, 2004, following reports of myocardial infarction and stroke) [4, 14, 16]. Such events continue to shape medicines safety regulation.

The continuance of such iatrogenic events despite the development of stringent medicines regulation confirmed the need for the medicines safety community to shift from a reactive to proactive approach. Such proactive measures included the founding of the International Society for Pharmacoepidemiology (ISPE) in 1989, an international organisation which aims to provide a forum for, and advocacy of, the field of pharmacoepidemiology, and the European Society of Pharmacovigilance (later to evolve into the International Society of Pharmacovigilance, ISoP) in 1992, which aims to promote the science of pharmacovigilance, and 'enhance all aspects of the safe and proper use of medicines' [7, 17, 18]. Most recently, the European Medicines Agency (EMA, established in 1995) developed 'Good Pharmacovigilance Practices' (GVP) as a key deliverable of the European Union (EU) overhaul of pharmacovigilance processes in 2010 (Directive 2010/84/EU).

GVP constitutes a set of measures designed to facilitate the performance of pharmacovigilance in the EU [19].

In addition to the above initiatives, there has been a growing interest in open access pharmacovigilance training resources. As of 2022, organisations including (but not limited to) the WHO, UMC, EMA, and MHRA all offer or share free online training resources dedicated to improving pharmacovigilance awareness and education [20-23].

2.2 The Importance of Pharmacovigilance in Healthcare Systems

As introduced above, pharmacovigilance is an essential public health tool for the prevention of medicines-related harm.

Several studies have aimed to assess the clinical and economic burden of AEs, and whilst figures vary according to context, the burden of AEs is universally agreed to be considerable. In 2011, the Strengthening Pharmaceuticals Programme (SPS) reported that in the US, Adverse Drug Reactions (ADRs) represent the fourth-to-sixth leading cause of death, and estimated that 197,000 deaths occur across the EU annually as a result of ADRs [24]. ADRs are frequently reported to be a significant cause of hospital admissions (between 4.2-30% in the US) and an important factor in determining the length of hospital stay (ADRs have been found to occur in 10-20% of hospital inpatients in the UK). An increased incidence and severity of ADRs is often reported in vulnerable populations (eg children and the elderly) [25, 26].

The annual economic burden of ADRs has been estimated to be US$168 million in Singapore (almost 5% of annual healthcare expenditure), £466 million in the UK, €79 billion in the EU, and between US$30.1 - 177 billion in the US [24-27].

To be effective, pharmacovigilance activities must take place at all stages of a medicinal product's life cycle. Premarketing safety evaluation, including toxicity studies, is essential to outline the safety profile of a novel drug, and a legal requirement for marketing authorisation approval. Nevertheless,

clinical trials typically lack the capacity to identify rarer ADRs; most involve a limited number (rarely no more than 5000) of homogenous participants (typically young, healthy, white males) and are conducted for a limited time span. Vulnerable populations, including children, the elderly, and pregnant and breastfeeding women, are rarely included in clinical trials. Postmarketing surveillance, the monitoring of medicines safety after marketing approval, is essential to consolidate a medicinal product's safety profile and identify rare and serious AEs [1, 28, 29].

It is clear that in the absence of strong pharmacovigilance systems, the risk of medicine-related harm to a population is greatly increased. Furthermore, weak systems result in a decrease in public trust and confidence in healthcare services. There is therefore a clear need to support the conduction and advancement of medicines safety activities in regions with limited pharmacovigilance capacity.

3 Contextualising Global Health Research

When seeking to address health inequity, global health researchers employ a myriad of umbrella terms to describe locations with lower health care/research capacity. The more common descriptors include 'Developing Country', 'Low and Middle-Income Country'* (LMIC), 'The Global South', 'Majority World', 'Low-Resource Setting' (LRS), 'Low-Resource Country', 'Resource-Constrained Setting', 'Resource-Constricted Country' and 'Resource-Limited Country'. These terms are often used interchangeably, despite the variations in the theoretical frameworks that underpin them.

Each of these labels is not without critique, which primarily concern the choice of metric(s) used to determine classification and/or potentially controversial connotations of the terminology [32, 33].

*Variants include 'Low-to-Middle-Income Country', and a distinction between 'Low-Income Country' and 'Middle-Income Country'. The World Bank/Organisation for Economic Co-operation and Development (OECD) Development Assistance Committee (DAC) list of Official Development Assistance (ODA) recipients also distinguish between 'Lower Middle-Income Country' and 'Upper Middle-Income Country' [30, 31].

For example, recent discussions have seen an increased awareness that the terms 'Developing Country'[*] (usually defined using the Human Development Index), and those employing a hierarchical category (eg 'Low') imply a divided 'us and them', in-group and out-group mindset, or that they perpetuate unequal colonial power relations by inferring the superiority of some regions over others; 'Developing Country' vs 'Developed Country', LMIC vs 'High-Income Country' (HIC), 'The Global South' vs 'The Global North' etc.

Other terms, namely those that include geographical qualifiers such as 'country', risk exaggerating (in the case of LMICs) or masking (in the case of HICs) regional inequities to/at a national level. It is important to consider that sub-national, regional variations in capacity (eg regional variations in infrastructure development, financial investment, human resource capacity, etc) are not necessarily reflective of the national picture. Accordingly, it is possible for a LRS to exist in an HIC, and for a High-Resource Setting (HRS) to exist in an LMIC [34].

One of the most widely utilised categories in global health research, 'LMIC' relies solely on an economic statistic, Gross National Income (GNI) per capita, to indicate development[†]. Whilst economic capacity will have an obvious impact on potential national healthcare expenditure, and thus national healthcare capacity, it is important to consider the multifactorial nature of healthcare determinants [30, 31, 35].

The terms 'Global South' and 'Majority World' represent a shift in rhetoric from the more traditional labels, as both seek to emphasise political inequities in addition to economic inequities,

[*]For the numerous reasons described, the terms 'Developing/Developed Country' and 'Developing/Developed World' were phased out of World Bank publications or databases from 2016. The United Nations (UN) continues to use the term 'Developing' in some of its country groupings, albeit with additional qualifiers, eg Least Developed Countries (LDC), Landlocked Developing Countries, and Small Island Developing States (SIDS).

[†]This is true of the World Bank Classification, however the OECD DAC list of ODA recipients, which is also used as a reference list of LMICs, highlights 'Least Developed Countries' as defined by the UN (which in turn are defined by the Human Assets and Economic and Environment Indices, in addition to GNI per capita) and also considers political factors (eg EU and/or G8 membership) [30, 31] .

specifically, in the case of 'Global South', encompassing regions and populations that hold 'marginal positions within global systems of decision making' [36]. The term 'Majority World' has also seen increasing use, and seeks to emphasise that the populations inhabiting 'underdeveloped' regions represent the vast majority of the world population.

Whilst demonstrating an important consideration of socio-political factors affecting development, the broad nature of these terms risks the generalisation of an extremely diverse range of populations. In addition, the abstract nature of these terms may be a source of confusion amongst a lay audience. The terms 'Global North/South' for example, have been accused of being misleading; some countries in the global geographic, 'Hemispheric North' are grouped in the 'Global South' (eg Bosnia and Herzegovina), and vice versa (eg Australia). In the case of the Majority World, it's 'boundaries' are at present, poorly defined. Proposed Majority World groupings include 'Africa, Asia, Latin America and the Middle East', or regions previously described as 'The Third World', whilst others sources point to either 'The West' or G8 members as the contrapuntal 'Minority World' [37, 38].

As with 'Majority World', it is clear that without a robust definition, some terms risk ambiguity. The use of the vague descriptors 'Constrained' or 'Limited', as opposed to the more-quantifiable 'Low', makes it harder to contextualise a 'Resource-Constrained' or 'Resource-Limited' setting in comparison to a LRS.

Given the range of existing terms and the variation in their underlying frameworks, the importance of a consideration of the multifactorial nature of health-related capacity determinants, the necessity of a sensitive and reflexive consideration of healthcare context, and the risks associated with assumptions on the interoperability and generalisability of these terms, Van Zyl et al acknowledge the value of a 'considered description of the research setting' when conducting global health research [32].

3.1 Defining a Resource

The precise definition of a 'resource' and the exact nature of the assets to which the term can be applied are context-dependent. In a health-related context, resources can be broadly categorised as 'the means available in a health system to deliver services to the population' [39]. This includes, but is not limited to, funding, infrastructure (eg institutions, communication networks, utilities, transport systems, etc), materials or supplies (eg medicines, consumables, equipment, etc), human resources (workforce capacity) and knowledge resources (education and training tools, context-specific information) [32, 34, 40].

A thorough consideration of health system resources should acknowledge necessary resources across the entire healthcare spectrum, including research and development, healthcare delivery, and policy decisions.

3.2 Defining a Low-Resource Setting

As discussed above, 'Low-Resource Setting' is one of a number of umbrella terms used in global health research to describe locations with comparably lower health care/research capacity. The term has no universally-agreed definition, and is not quantified by specific criteria or indices. Instead, by associating capacity broadly with resource availability, the term affords researchers the flexibility to define context-specific capacity determinants. The term, and its analogous variants ('Resource-Constrained Setting', 'Resource-Limited Setting', 'Resource-Limited Country', 'Resource-Constricted Country' and 'Low-Resource Country') also demonstrates a shift in rhetoric from other umbrella terms, by avoiding the implication that individual factors (economic, political, geographic or population-based) are primary capacity determinants.

Perhaps the broadest definition of an LRS in a healthcare context, as offered by Lahariya, would be '*A health system which does not meet the accepted norms for healthcare*' [39]. More detailed definitions would include standards for the 'accepted norms', which may include quantifiable measurements of one of more of the resources listed above (see **3.1**). In addition to resource

availability, van Zyl et al's recent scoping review identified nine interrelated themes characteristic of LRSs, which in addition to the lack of specific resources, also included suboptimal healthcare service delivery, geographical and environmental factors and the influence of local beliefs and practices as common components of LRSs [32].

It is clear therefore, that the multifactorial considerations make it difficult to provide a comprehensive universal definition of an LRS. Researchers who employ the term should do so with consideration of its context-specific nature, with a deep understanding of the relevant resources in their field, and where possible, define the scope of the term within their research context.

4 Communities of Practice

4.1 Theoretical Background

The term 'Community of Practice' (CoP) was first coined by anthropologists Lave and Wenger in their seminal 1991 work *'Situated Learning: Legitimate Peripheral Participation*' [41]. *Situated Learning*, and its namesake theory of social learning, is widely considered to represent a paradigm shift in learning theory, away from the classical, or 'standard' paradigm that includes behaviourism and cognitivism [42]. In contrast to these individual-focused, 'acquisition-based' (see below) traditional theories, situated learning theory dictates that active social participation is the central condition for learning [43]. For a visual comparison, see **Table 1**.

An alternate explanation of situated learning theory, and its deviation from classical learning theories, is offered by two contrasting 'metaphors of learning', the 'acquisition' metaphor and the 'participation' metaphor [44]. Classical theories can be considered to be models of knowledge acquisition; knowledge takes the form of a codified product (facts, figures, etc, with knowledge assessed via traditional examination), which is transferred in a unidirectional manner from teacher to student, and can be conceptualised as 'the individual mind being steadily stocked with ideas'

Paradigm	Standard/Classical	'Emerging'
Example Learning Theory	Behaviourism/Constructivism	Situated Learning
Metaphor of Learning	Acquisition	Participatory
Unit of Analysis	Individual	Community
Example Learning Loci	Classrooms/Schools	Communities of Practice

Table 1: A comparison of learning theories, their associated paradigms, and metaphors of learning.

[43, 45]. Contrastingly, situated learning can be described as a participatory theory; learning results from participation in a community structure and has no definable end point, with the group, or collective, the important unit of analysis, as opposed to the individual [43, 44].

Whilst situated learning provides an umbrella concept of social learning, Lave and Wenger proposed that CoPs are the loci in which situated learning takes place, as opposed to traditional 'institutional' notions of learning loci (classrooms, schools, universities etc) [46].

4.2 Defining a CoP

Wenger et al define a CoP as:

> *'A group of people who share a concern, a set of problems, or a passion about a topic and who deepen their knowledge and expertise in this area by interacting on an ongoing basis*' [47]

A CoP functions as a model of learning, in which learning takes place via the sharing of experience and tacit information, by encouraging discussion from multiple perspectives and by allowing the community's members to dynamically respond to the evolution of their field. Such activities foster 'identify formation' amongst community members, which Lave and Wenger argue facilitates

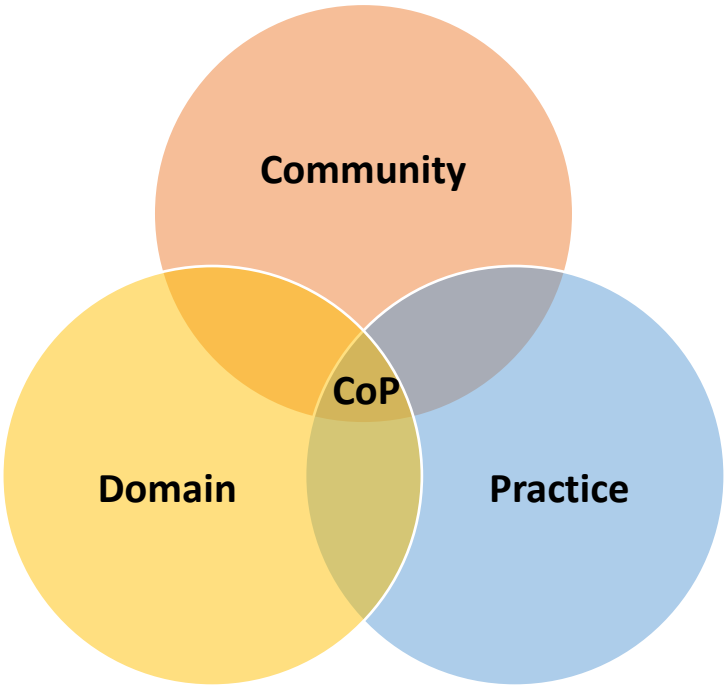


Figure 1: The structural elements of a CoP, as proposed by Wenger et al [47]. 'Community' describes the social fabric of the knowledge system; 'Domain' represents the common ground or 'shared interests' of the CoP members; 'Practice' describes the knowledge and activities that the CoP members share or develop.

learning through the creation of 'knowledgeable practitioners', or full members of the community [41, 43].

In *Situated Learning*, the CoP concept was abstract and ill-defined. Wenger later expanded the concept in-depth from a primarily managerial perspective, and developed a framework to guide the conceptualisation and evolution of a CoP. This framework identified three key elements of a CoP: Community, Domain, and Practice (**Fig. 1**) [47].

Building on Wenger's work, and seeking to define the 'boundaries' of a CoP, Hodkinson and Hodkinson identified two interpretations of the 'social-spatial delineation' of a CoP, 'Broad' and 'Narrow'. A broad perspective, offers 'elasticity and adaptability', and acknowledges that CoPs may exist within or around other manifestations of CoPs, as exemplified by their 'Russian doll' metaphor. Alternatively, a narrow perspective would focus on 'tightly knit', small CoPs with a focus on the CoPs immediate activities [48].

4.3 CoPs in Healthcare

Since its inception, CoP theory has been applied in a variety of fields including business, academia, government, and more recently, interactive technologies such as social media [47, 49-52]. In addition, CoP theory has seen frequent adoption in the field of healthcare. A healthcare context presents a logical environment to adopt a CoP approach, thanks to the multiplicity of stakeholder settings (varying clinical settings, research and development, regulation, etc), the diversity of stakeholder knowledge and skillsets across different specialities, the intricate complexities of the field of medicine and the involvement of workplace learning in many clinical training programmes [53, 54]. Moreover, the flexibility of the CoP concept lends itself well to the dynamic nature of healthcare practices [55].

4.4 CoPs in Pharmacovigilance

Both a formal literature search and lay internet search return little in the way of 'Pharmacovigilance Communities of Practice'[*]. Nevertheless, as previously alluded to (see **2.1**), group-based medicines safety knowledge-generation initiatives do exist. The international non-profit societies ISoP and ISPE both support groups of members who seek to further safety-based activities in defined regions, themes, or populations, varyingly termed 'Chapters', 'Special Interest Groups' (SIGs) and 'Regional Interest Groups' (RIGs) [18, 56, 57]. Other organisations including the WHO, EMA, Council for International Organizations of Medical Sciences (CIOMS), European Contract Research Organisation Foundation (EUCROF), Developing Countries Vaccines Manufacturers Network (DCVMN), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and Drug Safety Research Unit (DSRU) host international, pharmacovigilance-related 'working groups' [58-64] .

[*]Trial searches using the search strategy adopted in the 'Pharmacovigilance in LRSs' literature search, with an additional theme of 'Communties of Practice', using the search term 'communit* of practice' returned no results. A lay internet search (Google) using search terms taken from each of these three themes, and reviewing the first 10 pages, also returned no results specific to LMICs.

Whether or not these groups consider themselves to be CoPs and/or whether they could be described as a CoP according to the various interpretations of the concept, will not be examined here. Such classification would depend on the particular definition of a CoP each group wished to adopt, and upon the specific context in which the group operates. Regardless of individual interpretations, most, if not all of these groups present some additional barrier to group membership in addition to the loose 'membership requirements' summarised by Wenger as '*…people who share a concern, a set of problems, or a passion about a topic'* (see **4.2**). Some, for example, require a financial contribution (eg annual subscription fees), whilst the membership of others is drawn exclusively from highly-experienced members of the field.

4.5 The Global Health Network

Founded in 2010, The Global Health Network (TGHN), is a knowledge-sharing, research methodology and capacity development initiative which aims to support health research in regions and disease areas where evidence and data are lacking. The platform operates via two integrated elements; facilitating the activity of 'Knowledge Sharing Hubs' to enable knowledge exchange and raise engagement in global health research activities, and alongside this, delivering research capacity development through teaching, training, and career development by providing open-access guidelines, tools and resources [65].

TGHN's interconnected network of Knowledge Sharing Hubs operate as an 'open online science park'. Each is coordinated via a different consortia, organisation, network, programme or research team and is focussed on building research capacity in a particular region, disease area, or global health discipline. The hubs function as platforms for knowledge exchange, where stakeholders can share 'data, guidance, methods, and experience', and offer an 'open, neutral and collaborative workspace where researchers and teams can contribute and others can find examples of good practice to build from'. The aim is for each hub's activities to be driven by its membership [66].

As of 2021, TGHN had over 400,000 registered members worldwide, and supported 51 Knowledge Sharing Hubs, each focussed on building capacity in a diverse range of global health research areas. The platform has received over 40 million views since its inception, over half of which (21 million) have been from Africa, Latin America and the Caribbean and Asia. Over two million TGHN online training modules had been taken, and there have been 500,000 downloads of research templates, tools and resources featured across the platform [66].

4.6 Global Pharmacovigilance

Global Pharmacovigilance (globalpharmacovigilance.org, GPV) is a constituent Knowledge Sharing Hub of TGHN. Launched in mid-2016, the platform aims to support pharmacovigilance activities in LRSs around the globe. GPV hosts a broad range of pharmacovigilance-related information, including notices of events, training and education opportunities, news items, links to pharmacovigilance organisations, institutions and societies, and a growing number of articles on relevant topics. The hub is jointly coordinated between the University of Cape Town, South Africa, and the University of Oxford, UK.

Despite some initial seed funding, coordination of GPV remained a largely voluntary endeavour and prior to 2018, there has been limited opportunity to develop or co-develop resources to address pharmacovigilance knowledge gaps. Nevertheless, GPV was consistently one of the top five most-accessed member hubs within TGHN, and as of 2018, had nearly 3000 members globally. In addition, GPV maintains an active social media presence and manages both a YouTube channel and an active Twitter account.

4.7 Global Pharmacovigilance: A Pharmacovigilance CoP?

The existence of a group of individuals with a shared interest in global pharmacovigilance activities presented an opportunity. Via the application of the CoP model (**Fig. 2**), it was proposed that the

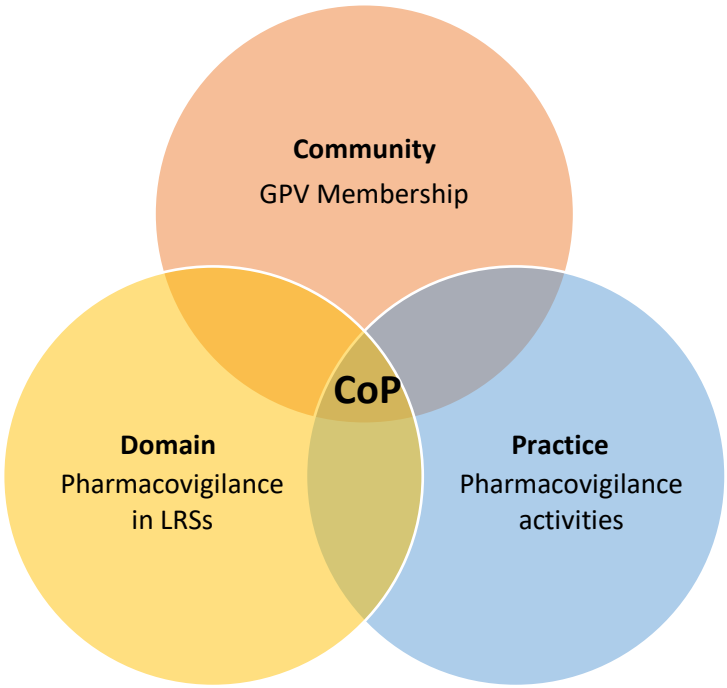


Figure 2: Constituent elements of this research within the CoP model.

collective knowledge and experience of the GPV membership could be harnessed, by inviting members to work together as a CoP on specific challenges facing pharmacovigilance in LRSs. In particular, members would be invited to work together to identify the highest priorities for pharmacovigilance in LRSs, and to collectively develop relevant training, guidance, tools and/or resources to address the challenges identified, using the online environment as the workspace for discussions, networking and dissemination of outputs.

5 Aims of this Thesis

Following consideration of the above factors, this thesis aimed to identify how and whether the immediate challenges facing pharmacovigilance in LRSs can be addressed by harnessing the collective knowledge, skills and experience of a pharmacovigilance CoP. The specific aims of this thesis were defined as follows:

- To assess whether the membership of an online pharmacovigilance platform can operate as a CoP.
- To investigate whether this CoP can work together to identify the current priorities for pharmacovigilance in LRSs, and develop resources to address these challenges.
- To measure the impact of these resources on the work of those engaged in pharmacovigilance activities in LRSs.

Specific objectives of individual research activities, outlined in the following chapters and determined in an iterative manner following the action research approach (see **11.2**) were as follows:

Knowledge Synthesis

- To provide a comprehensive overview of the pharmacovigilance landscape in LRSs, via the identification of relevant published literature, and existing training and education resources.
- To identify the major challenges facing pharmacovigilance in LRSs.

Survey

- To identify and prioritise pharmacovigilance knowledge gaps in LMICs, with specific relation to the COVID-19 pandemic.

- To gather demographic data in order to better understand the population that makes up the pharmacovigilance CoP.
- To assess attitudes towards pharmacovigilance within the pharmacovigilance CoP.
- To gather data on the usage and user experience of GPV.

Workshop

- To present the findings of the survey to the CoP.
- To facilitate discussion of the highest pharmacovigilance priorities identified by the CoP, their relevance to the CoP member's setting, and to elucidate further information on the precise aspects of these priorities that are areas of concern.
- To gather further consensus on the CoP's top priorities for pharmacovigilance.
- To provide an overview of GPV to the CoP.
- To communicate the intention to form working groups to address the top-rated priorities identified in the workshop.

Working Groups

- To establish collaborative working groups focussed on the priorities for pharmacovigilance in LRSs identified in the previous consensus-building activities (survey and workshop).
- To facilitate further in-depth discussion on the priorities identified, expand the topics, and elucidate the challenges and bottleneck within those themes.
- To incentivize discussion on potential solutions to these challenges.
- To support the development of resources and interventions to address these challenges.
- To assess the impact of these resources and interventions when possible.

II Knowledge Synthesis

6 Rationale

Knowledge synthesis activities were undertaken to provide a comprehensive overview of the pharmacovigilance landscape in LRSs, via the identification of relevant published literature, and existing training and education resources. In turn, it was envisaged that this would identify the major challenges facing pharmacovigilance in LRSs, and provide focus for future research activities.

7 Methods

A novel two-stage knowledge synthesis strategy was adopted. A traditional literature search was undertaken to identify relevant peer-reviewed published literature regarding pharmacovigilance in LRSs. In addition, an experimental scoping review, employing a specialist search software was conducted to identify available free and costed online resources and grey literature designed to aid researchers and Healthcare Professionals (HCPs) in improving pharmacovigilance practice, knowledge, and research in LRSs.

Due to the experimental nature of this scoping review, and the aim to identify all relevant training and educational resources (e-learning courses, toolkits, webinars etc) as opposed to purely literature (published or grey literature) the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist was consulted, but not adopted as a core tenet of this review [67]. A further discussion of the rationale behind this decision, and its impact upon the finding of this experimental scoping review, is discussed in **8.4**.

7.1 Literature Search

The literature search was first conducted in June 2019. The aim was to comprehensively identify recent publications regarding pharmacovigilance in LMICs, from which publications that focused on knowledge exchange could be identified and highlighted. A search strategy was designed,

focussing on two major themes; Pharmacovigilance and LRSs (**Appendix 1**). Results were limited to publications post-2016 (previous three years), to ensure the most relevant and up-to-date results were returned, and English language publications.

The search strategies were designed with the support of a University of Oxford Nuffield Department of Medicine Outreach Librarian. The search was run on the biomedical and pharmacological bibliographic database Embase and was repeated on a quarterly basis to identify newly-published relevant literature. Search results were exported to the reference management software Endnote X9 (vX9.2) for screening and management. Bibliographies of relevant publications were then examined to identify additional relevant publications.

7.2 Rapid Resource Scoping Review

A specialist 'search assistant' software, DEVONagent Pro (v3.11.1), was utilised to conduct an online 'meta-search' to query multiple search engines ("plugins") simultaneously. The search engines included in the queries were; Bing, Google, Google (PDF), Yahoo!, Google Video, YouTube, Medline Plus, PubMed, WebMD, Google Scholar (Articles), and JSTOR*. Up to 200 results per plugin were collected during each search.

Trial searches were undertaken to guide the design of an appropriate search strategy. Initial searches were conducted using combinations (using the Boolean operator AND) or individual examples of the keywords described in **Table 2**. Terms were either searched individually or in combination, to assess the number of relevant results returned and ensure compatibility with the DEVONagent Pro software. Keywords were grouped by theme, with those included in themes one and two ('PV' and 'LRSs' respectively) selected based upon their inclusion in the literature search strategy (**Appendix 2**). Keywords in theme 3 ('Resource') were selected to cover a wide range of

*Although a traditional literature search had been completed using the bibliographic database Embase, the scoping parameters also include searches of scientific databases (PubMed) to allow for the identification of literature that was, for whatever reason, not revealed in the literature search.

potential learning materials. Results of these trial searches were reviewed to assess their relevance to the search aims. Keywords that were identified as superfluous or those that returned largely irrelevant results in these trial searches were removed or amended to refine the search strategy.

During the process of refinement, 18 'general' searches were run using the search terms listed in **Table 3**. The general search terms included individual searches of remaining keywords in theme one (PV) to guide that theme's further refinement, as well as exploratory searches combining search

Theme 1: Pharmacovigilance	Theme 2: LRSs	Theme 3: Resource
postmarketing surveillance	developing countr*	educational tool*
pharmacovigilance	low income countr*	e-Learning
drug surveillance	low-income countr*	"formal guidance"
drug monitoring center*	middle income countr*	guid*
drug monitoring centre*	middle-income countr*	"standard operating procedure*"
drug monitoring program	low middle income countr*	SOP
international drug monitoring	low-middle income countr*	tutorial*
medicine* safety monitoring	low and middle income countr*	template
adverse drug reaction* monitor*	Africa	tool*
adverse drug* reaction* report	Asia	video*
	South America	lecture*
	Latin America	seminar*
	Central America	webinar*
	lmic*	course
	developing world	
	lami countr*	
	resource limited countr*	
	resource poor countr*	

Table 2: List of trial keywords used to guide final search strategy. Terms were either searched individually or in combination, to assess the number of relevant results returned and ensure compatibility with the DEVONagent Pro software.

Search Terms
"postmarketing surveillance"
pharmacovigilance
"drug surveillance"
"drug monitoring"
"international drug monitoring"
"drug monitoring program"
"medicine* safety monitoring"
"adverse drug reaction monitor*"
"adverse drug reaction report*"
"pharmacovigilance in africa"
"pharmacovigilance in developing countr*"
"postmarketing surveillance in developing countr*"
"postmarketing surveillance in africa*"
"africa* drug monitoring program"
"africa* drug monitoring"
medicines safety in africa
african drug monitoring program
pharmacovigilance in developing countries

Table 3: List of 18 search terms used to refine the search strategy. Results from these searches were included in the final analysis.

Theme 1: Pharmacovigilance	Theme 2: LRSs	Theme 3: Resource
"postmarketing surveillance"	"developing countr*"	education*
pharmacovigilance	"low income countr*"	guid*
"adverse drug reaction report*"	"middle income countr*"	learning
	Africa	"standard operating procedure*"
	lmic*	SOP
	"resource limited countr*"	tutorial*
	"resource poor countr*"	template
		tool*
		video*
		lecture*
		seminar*
		webinar*
		course

Table 4: List of keywords used during the scoping exercise. Phrasing examples: (i) using the first set of terms: ("postmarketing surveillance" AND "developing countr*" AND education*) (ii) using the last set of terms: ("adverse drug reaction report*" AND "resource poor countr*" AND course).

terms from themes one and two. In-depth screening of the results of these general searches, involving the removal of irrelevant results, duplicate results and literature previously identified in the literature search, guided the development of a final search strategy (**Table 4**), as terms returning few or no relevant results were removed.

For the scoping exercise-proper, 273 three-level queries were run in DEVONagent Pro using the search terms in **Table 4**. Results were screened and irrelevant results, duplicate results, and literature previously identified in the literature search were removed prior to analysis. Any relevant journal articles that were identified and which had not been highlighted in the first literature search were exported to a reference management software (Endnote X9). After review in DEVONagent Pro, data was processed using MS Excel.

8 Results

Findings of the literature review are presented below.

8.1 Pharmacovigilance in LRSs: An Overview

Whereas the thalidomide tragedy spurred advances in pharmacovigilance systems across affected countries (see **2.1**), this surge of progress was not echoed across the vast majority of LMICs. This was largely due to a lack of available medicines, weak healthcare systems and historical financial considerations, as many LMICs were not regarded as a viable market by the pharmaceutical industry at the time* [7, 70].

*Thalidomide (marketed as a sedative) was distributed in some LMICs, but only on a very small scale. It received more widespread usage in LMICs as part of combination formulations, such as the anti-infective and antidiarrhoeal 'Entero-Sediv', however these formulations typically contained only a low dose of Thalidomide [68]. Despite little-to-no locally reported incidences of thalidomide-associated phocomelia, the thalidomide disaster did spur the development of medicines regulation in a minority of LMICs, such as the Medicines and Related Substances Control Act (101) passed in South Africa, 1965. Despite the introduction of this regulation, it has been suggested that 'The South African State has never been able to meet fully its obligations in terms of providing access to safe pharmaceuticals' [69].

Few LMICs joined the WHO PIDM (see **2.1**) prior to 1990[*]. By contrast, >30% of all HICs (and >40% of all non-SIDS HICs) had achieved full membership of the programme by 1991 (see **Fig. 3**). The overwhelming majority of pharmacovigilance systems in LMICs have therefore either been established, met the minimum requirements to join the PIDM, or mustered the political will to join the PIDM only in the past 30 years, and are consequently largely nascent. In addition, nearly 70% of the current Associate Members of the PIDM (considered to be in the early stages of establishing their pharmacovigilance systems having not yet fulfilled the requirements for full membership) are LMICs [29, 71].

Due to the slow uptake of pharmacovigilance activities in LRSs, the vast majority of global ADR data has emerged from High HRSs, where the preponderance of global pharmaceutical development capacity is concentrated. Nevertheless, variances in genetic, physiological, cultural, and socio-behavioural factors mean that this data is often not generalizable to populations in LRSs [29].

Antimalarials provide a good example of the enormous paucity of locally-generated pharmacovigilance data in LRSs. An assessment of global reports of adverse reactions to antimalarials found that Sub-Saharan Africa, a region which contributes to 86% of estimated malaria cases and 91% of estimated malaria deaths, has submitted less than 2% of all ICSRs involving antimalarials to the PIDM since 1968 [72]. Moreover, Ampadu et al determined that as of 2015, of the global total of ICSRs submitted to the PIDM since 1968, only 0.88% have been submitted from Africa [73].

The lack of medicine safety activities in LRSs has led to avoidable examples of significant medicines related harm, where lessons learnt in HRSs were not implemented in LRSs. In 1937, the 'Massengill incident', (where 'Elixir Sulphanilamide', a liquid formulation containing 70% toxic solvent

[*]There are three countries listed as LMICs by the World Bank in 2022 that became full members of the PIDM pre-1990; Bulgaria (1975), Thailand (1984) and Türkiye (1987). Indonesia and Malaysia both joined the PIDM in 1990.

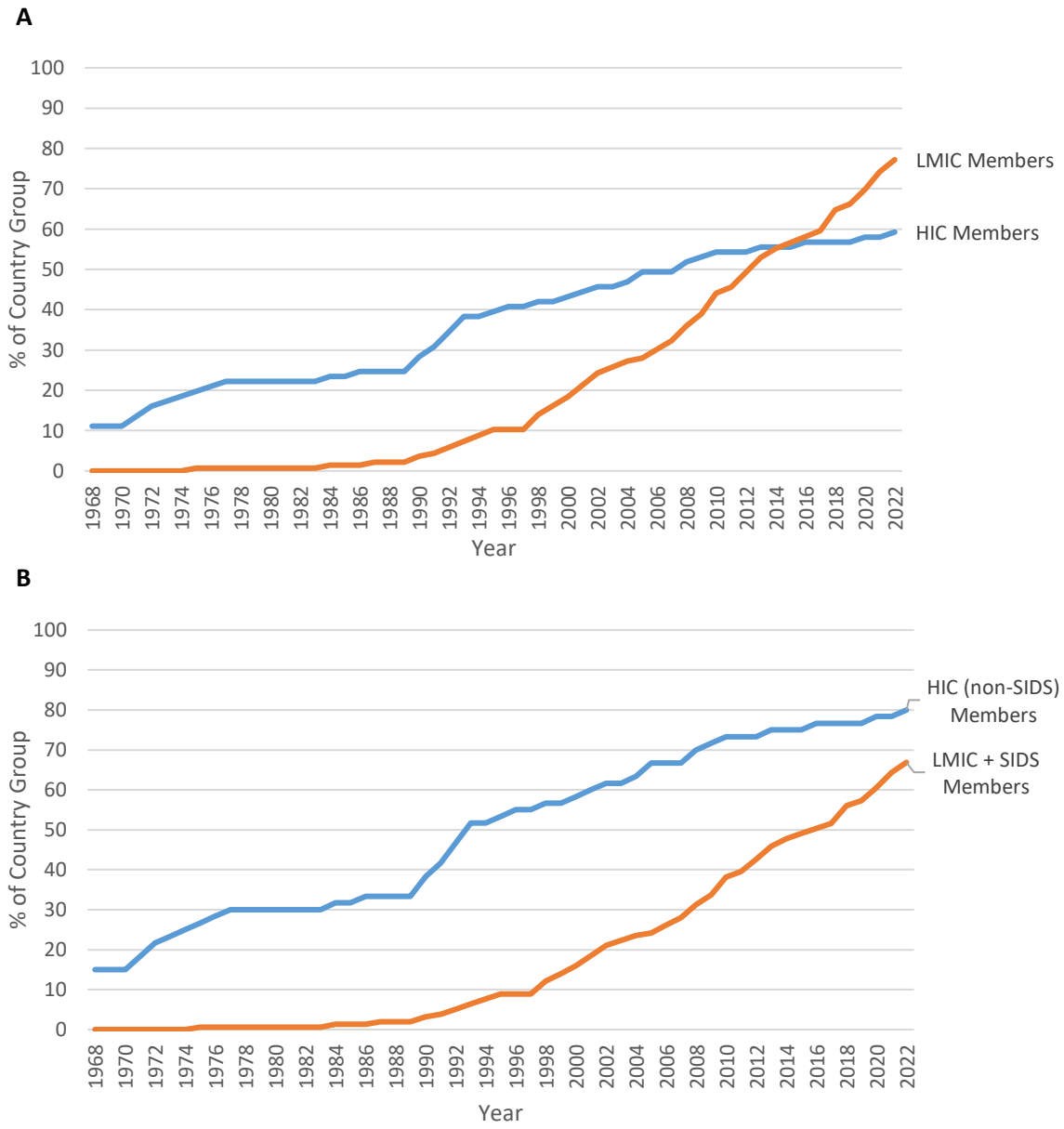


Figure 3: An economic (A) and 'alternative capacity' (B) comparison of WHO PIDM full member countries over time. Data taken from the World Bank Country and Lending Groups Classification 2022, the WHO PIDM and the UN Office of the High Representative for the Least Developed Countries, Landlocked Developing Countries and Small Island Developing States (UN-OHRLLS). Note that this figure does not account for historic variations in classification, such as economic classification at the time of achieving full membership of the PIDM. Data for historical sovereign states are also not considered. For example there were 10 founding members of the PIDM, but data for one of the founding countries, Czechoslovakia, is not considered here due to its dissolution in 1992. Data for Czechia and the Slovak Republic (established following the dissoultion of Czechoslovakia, both current HICs) is included. Both became full members of the PIDM in 1992 and 1993 respectively. As of 2022, country group totals are as follows: HICs = 81, LMICs = 136 (World Bank).

Of the HICs that are Associate or non-members of the PIDM (as of 2022, n=33), 63.6% (n=21) are classified as a SIDS by the UN-OHRLLS (see also **3**). Despite their high economic classifications, these nations are listed by the UN as 'Vulnerable Member States' due to their '*unique social, economic, and environmental challenges*', and provide a good example of how reliance upon purely economic statstics may obfuscate the true capacity of a particular setting. In **B**, LMICs and all SIDS (including HIC SIDS) are grouped to provide an an example of how consideration of mutiple capacity determinants impacts perspectives on capacity inequities.

diethylene glycol [DEG] caused the deaths of an estimated 105 people, including 34 children, in the US) led to the passing of the Federal Food, Drug, and Cosmetic Act, laying concrete foundations for modern-day medicines regulation in the US [4, 74]. Despite this tragedy, repeated incidences of fatal medical product DEG contamination have been observed in LRSs since 1965, including in Nigeria (1990 and 2009, at least 47 and 84 deaths respectively), Haiti (1995-1996, at least 90 deaths) and Bangladesh (1990-1992, at least 236 deaths suspected). In these incidences, the vast majority of (if not all) fatalities were children [29, 75-77][*].

Despite the slower implementation of pharmacovigilance activities in LMICs, steady progress has been made, and a number of organisations have established initiatives to support the strengthening of pharmacovigilance systems in LRSs [78]. Nevertheless, there is still a large disparity in comparison to the progress in HRSs, and only a small number have established a national pharmacovigilance policy [79]. A recent systematic review of '*Pharmacovigilance Systems in Developing Countries Using the WHO Pharmacovigilance Indicators*' found system performance to be low in all countries examined [80]. This lack of medicines safety activities poses an enormous risk to the populations in these settings.

8.2 Pharmacovigilance in LRSs: Current Challenges

The challenges facing pharmacovigilance in LRSs are manifold and multidimensional. Historically, medicines safety activities have not been seen as a priority in LRSs, as healthcare systems are typically overburdened, access to basic healthcare services and medicines is poor, infrastructures are weak, and budgetary support insufficient [81]. Pharmacovigilance systems that do exist are largely inchoate, and legislation and regulatory capacity is weak. In addition, political instability,

[*]Such incidences of medicines contamination have primarily been detected by spontaneous reporting (in historic occurrences such as the Massengill incident, via communications to medical journals or professional associations, in more recent occurrences, via formal national pharmacovigilance reporting channels) and/or by epidemiological investigations following the recognition of disease clusters in emergency care settings.

episodes of conflict, security concerns and natural hazards can dominate national agendas, and stall the process of healthcare capacity development.

Human resource pressures are a major constraint. Many LMICs have a small health workforce, and thus a high patient-to-HCP ratio. This results in overburdened HCPs with little time to report AEs or engage in pharmacovigilance activities [79, 82, 83]. These personnel constraints are exaggerated by 'brain drain', the migration of skilled healthcare workers, predominantly to HRSs [84]. Each of these factors contributes to a scarcity of dedicated pharmacovigilance personnel which is further compounded by the high turnover of local pharmacovigilance staff and a lack of training opportunities [29, 81, 83].

Limited financial resources are also a critical area of concern. The presence of a dedicated budget for pharmacovigilance has been associated with higher pharmacovigilance systems performance [80]. Despite this, a lack of budgetary support is consistently identified in the literature as a key barrier to improved pharmacovigilance capacity in LRSs [29, 81, 83]. Indeed, interruptions of funding have seen pharmacovigilance programs in LRSs suspended [85].

Low reporting rates are endemic, and a leading cause of the low-levels of pharmacovigilance data generation in LRSs (see **8.1**). Whilst attitudes towards pharmacovigilance practices in LRSs are generally found to be positive, awareness and knowledge of reporting systems amongst both healthcare professionals and the general public are generally found to be poor, and reporting habits are not ingrained [82, 86-89]. Limited reporting and follow-up activities can be exaggerated further by unreliable telecommunications coverage. Furthermore, a lack of legal clarity and protection means that data generation is often hampered by the hesitancy of HCPs to report AEs for fear of litigation [79]. The limited volume of reports means there is a low capacity for signal detection in LRSs, and the ability to identify significant local drug-safety issues is greatly hampered [81].

Cultural factors are also a significant consideration for pharmacovigilance stakeholders in LRSs. High levels of cultural diversity require that reporting tools often need to be available in a number

of local languages [79, 83]. This necessitates additional physical (eg reporting tools) and human (eg skilled translators) resources, of which the associated financial pressures will add to existing budgetary strains. Therapeutic cultures also differ from HRSs; LRSs, for example, often see a higher prevalence of self-medication and usage of traditional and herbal medicines [29, 79]. These practices are largely unregulated and present a number of challenges; the nomenclature of herbal and traditional medicines may vary widely, which can make data collection and analysis challenging; self-medication, or reliance upon unregistered traditional and herbal practitioners, is common, and hence pharmacovigilance systems which limit reporting to registered HCPs provide only a partial snapshot of potential harm; several common herbal medicines have known interactions with 'conventional' allopathic medicines; misidentification of medicinal plant species can lead to incidences of harm [3, 79, 81].

Less well understood is the impact of colonisation on pharmacovigilance capacity in LRSs, although some initial observations can be highlighted. Considering the Africa context, despite the existence of WHO Collaborating Centres (WHO-CCs) for pharmacovigilance in both Anglophone (Ghana) and Francophone (Morocco) countries (also, see below), and hence the existence of regional institutions able to deliver training in both languages, pharmacovigilance capacity generally appears to be greater in Anglophone countries [83]. The SPS for example, identified that in sub-Saharan Africa, *'countries with the most complete set of components for a comprehensive PV system happen to be Anglophone countries*' [90]. Similarly, more recent data published by Garashi et al suggests that pharmacovigilance system performance tends to be stronger in Anglophone sub-Saharan African countries than Francophone countries [80]. In a cross-sectional study of African pharmacovigilance systems performance, Bencheikh et al also noted that '*English speaking countries scored higher than countries that spoke neither English nor French*' [91].

These findings highlight pharmacovigilance capacity inequities across different LRSs, and shine a light on the potential impact of colonial histories on both regional pharmacovigilance capacity and

healthcare capacity in general. Whilst this remains an understudied field, it seems clear that non-Anglophone regions bear the greater burden of weak pharmacovigilance systems. This is further exacerbated by the predominant publication of training materials and guidelines in English at the global scale [79].

In addition to the above considerations, colonial histories may also impact variations in methodological approaches to pharmacovigilance, and the availability of safety information and data. For example, adoption of 'The French Method' for causality assessment (a particular feature of the French pharmacovigilance system) in LRSs appears to be concentrated in francophone North Africa (Morocco, Tunisia and Algeria) [4, 92]. Examples of overlapping pharmacovigilance activities between former colonies and former colonial powers, primarily the sharing of drug safety alerts (examples include France and Cote d'Ivoire, and France and Burkina Faso) also exist [93, 94]. The impact of these regional variations in methodological approaches, and postcolonial collaborations, on pharmacovigilance capacity in LRSs is uncertain.

Weak regulations, porous borders, and the associated costs of systematic national-level medicines quality testing mean that LRSs represent ideal environments for the proliferation of substandard and falsified (SF) medicinal products [24, 29, 95]. A recent systematic review estimated the prevalence of SF medicines in LMICs to be between 19-30% of all medicinal products [95]. Similarly, Nayyar et al have reported that up to 36% of antimalarial drugs collected in Southeast Asia were found to be falsified, whilst in sub-Saharan Africa, a third failed chemical assay analysis [96]. The prevalence of poor quality medicines poses a significant risk of harm to populations in LRSs, whether by direct iatrogenic harm, loss of confidence in healthcare systems, or (in the case of anti-infectives) the development of drug resistance.

A lack of robust policies regulating the contribution of the pharmaceutical industry to pharmacovigilance systems, and an associated lack of accountability on the part of pharmaceutical companies, is also common in LRSs [29]. In their examination of corporate commitment to

pharmacovigilance both internationally and in India, Moscou et al found that pharmaceutical company policies do not adequately feature pharmacovigilance as an integrated element [97]. Even where formal regulations do exist in LRSs, their impact on ICSR submissions to national databases, and the general compliance of pharmaceutical companies, has been questioned [81]. Indeed, in a comparative '*Analysis of Pharmacovigilance Systems in Five Asian Countries*' (all LMICs), it was concluded that '*The pharmaceutical industry's PV performance is below expectation in an already weak regulatory environment'* [90].

Pharmacovigilance systems that do exist in LRSs are commonly fragmented. There is often limited harmonisation of pharmacovigilance activities at both an international level, and across relevant national stakeholders including regulatory authorities, public health programmes and pharmaceutical companies. This fragmentation hinders data sharing, and data silos amongst organisations are common. Moreover, real time, raw safety data is rarely accessible to those outside of data collection organisations [83, 98].

In combination, the factors discussed above present a significant barrier to building pharmacovigilance capacity in LRSs. The precise challenges vary according to setting and in combination and can present individual profiles for particular regions. For example, a lack of regulatory harmonisation and lack of quality control measures curtail pharmacovigilance development across Africa [70, 83]. The spread of medicines safety misinformation has led to significant impacts on public confidence in healthcare systems in Southeast Asia [99, 100]. Limited infrastructure and the lack of capacity to generate significant numbers of reports are exaggerated by geographical factors in small island nations, such as Caribbean and Pacific Island Countries [82]. Nevertheless, the above factors are common to some degree across all LRSs.

Knowledge Exchange: A Key Issue?

The poor legislation and regulatory capacity, weak supply chains, vast majority of the global disease burden and the lack of financial, human and technical resources that have all hampered pharmacovigilance development in LRSs are further exasperated by the global lack of coordination, collaboration and knowledge exchange between all stakeholders working within pharmacovigilance [24, 70, 99, 101-103].

This is not to say that initiatives to foster knowledge exchange and build medicines safety capacity in LRSs do not exist. ISoP has regional Chapters (see also **4.4**) dedicated to pharmacovigilance in LRSs, including Africa, Latin America, the Middle East, South Asia, South Eastern Europe the Western Pacific. In addition it also supports SIGs, some of which (eg ISoP Herbal and Traditional Medicines SIG) are particularly relevant to pharmacovigilance in LRSs [18, 104]. Similarly, ISPE supports RIGs in Africa and Latin America [105].

The WHO currently supports three collaborating centres (WHO-CC, also see above) which include pharmacovigilance in their remit, two of which (Centre Anti poison et de Pharmacovigilance du Maroc, Morocco, and Pharmacovigilance Program of India, India) are based within LMICs and maintain a focus on building pharmacovigilance capacity in LRSs [106]. In Africa, The New Partnership for Africa's Development (NEPAD) African Medicines Regulatory Harmonisation (AMRH) programme has designated 11 medicines safety and regulatory organisations across the continent as Regional Centres of Regulatory Excellence (RCOREs), two of which (The African Collaborating Centre for Pharmacovigilance, Ghana, and the Pharmacy and Poisons Board, Kenya) have been designated RCOREs in pharmacovigilance. Free and costed online and face-to-face training courses are also provided by several organisations, although these may not be focused towards or be financially or geographically viable to those based in LMICs [107-110].

Despite this encouraging progress, many studies have indicated a need to increase human resource capacity and knowledge exchange to improve pharmacovigilance activities in LRSs. This research

often highlights the need to improve capacity by increasing the training of HCPs and availability of training resources [70, 79, 81]. Nevertheless, it has been suggested that the provision of pharmacovigilance training alone is not an adequate mechanism for developing pharmacovigilance capacity. One African based study identified 'social resources', including the ability to network with other national pharmacovigilance centres and 'build linkages' with all relevant stakeholders, as highly beneficial in exchanging knowledge and best practices, whilst also stressing that involvement with an organisation (such as the PIDM) which provides access to publications and training resources is a valuable asset [102]. Similarly, a review of the pharmacovigilance system in Vietnam suggested that to combat the limited pharmacovigilance practices of local healthcare workers, '*an efficient mechanism for exchanging ideas between stakeholders is needed*' [99]. In their editorial '*Pharmacovigilance in developing countries'*, Pirmohamed et al conclude that '*The lack of local expertise in pharmacovigilance*' could be addressed, amongst other methods, through '*the sharing of best practices*', and in their more recent report '*Pharmacovigilance in developing countries (part II): a path forward*', Elshafie et al describe knowledge sharing and collaboration as a '*key recommendation*' [103, 111]. It is clear therefore that to effectively build pharmacovigilance capacity in LRSs there is a need to not only address the limited access to training and education opportunities, but to build a collaborative professional network which allows continual support and sustainable knowledge exchange.

8.3 Rapid Resource Scoping Review Results

A total of 291 scoping searches (18 general searches and 273 three-level queries,) were run using DEVONagent Pro (see **7.2**), retuning a total 3,725 individual results (**Table 5**). Following screening, 43 search results (1.2%) were identified to contain educational resources or learning materials relevant to pharmacovigilance. Of these results, 38 (88.4%) were (or featured) free, open-access resources, whereas five (11.6%) were (or featured) paid training/postgraduate courses.

Search	Total Searches	Total Results	Relevant Results	Percentage Relevance of Total Results (%)	Relevant Results per Search (n)
General Search	18	1482	10	0.67	0.56
Three-Level Search	273	1793	33	1.84	0.12
Total	291	3725	43	1.15	0.15

Table 5: Resource scoping review search results breakdown. Percentage Relevance of Total Results = (relevant results/total results)*100. Relevant Results per Search = Relevant Results/Total Searches.

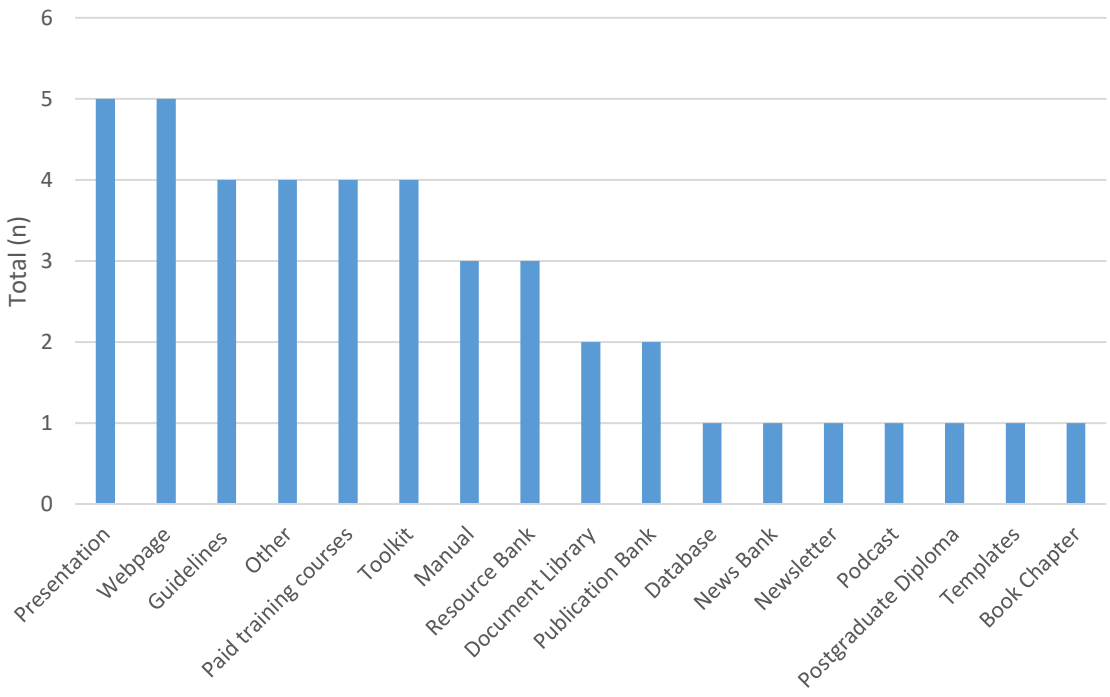


Figure 4: Types of resource identified during the scoping review. 'Other' describes resources or sources of information that could not be definitively classified. Costed resources included 'Paid training courses' (n=4) and 'Postgraduate Diploma' (n=1).

The most common type of resources identified were presentations and 'webpages' (basic, text-based, explanatory webpages) followed by guidelines and costed training courses (see **Fig. 4**).

Resources were found to come in a range of formats including downloadable documents, podcasts and searchable libraries and databases. The majority of resources identified were developed by, or in collaboration with the WHO (n=10), followed by the EMA, the United States Agency for International Development (USAID) and TGHN (each: n=3) (see **Fig. 5**).

Of the 43 results, 10 (23.3%) were identified following the 'general' search compared to 33 (76.7%) results for the three-level queries, duplicates discounted (see **Table 5**). Of the three-level queries, the search terms that returned the most results in their theme were as follows;

- **Theme 1, Pharmacovigilance**: 'Pharmacovigilance' (n=29, 87.9%)
- **Theme 2, LRSs**: 'Developing Count*' and 'Africa' (each: n=12, 36.4%)
- **Theme 3, Resource**: 'Education*' and 'Learning' (each: n=7, 21.2%)

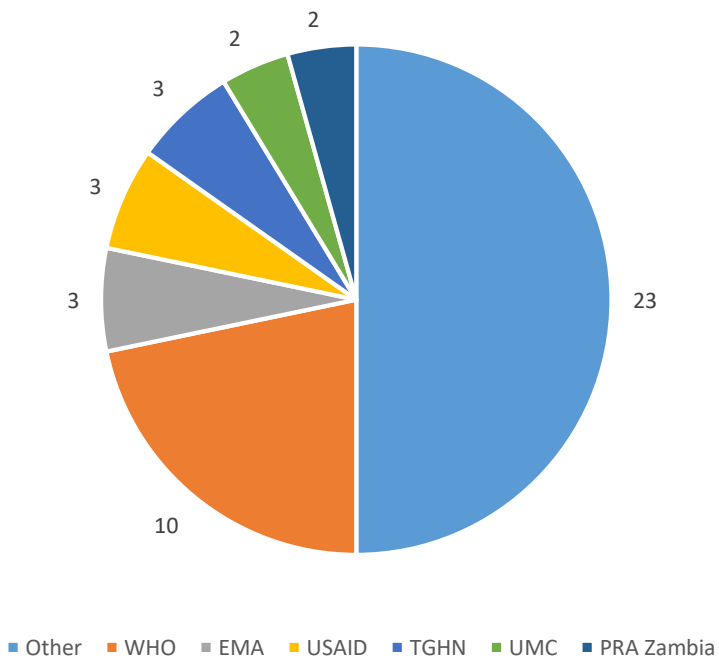


Figure 5: Institutions that developed resources identified in the scoping review (n). 'Other' (n=23) represents institutions that developed/collaborated on a maximum of one resource identified. See **Appendix 3** for a full overview of institutions identified. PRA Zambia = 'Pharmaceutical Regulatory Authority Zambia', renamed the Zambia Medicines Regulatory Authority (ZAMRA) in 2013.

See **Table 6** for a comprehensive overview of results according to three-level search term. In addition to the 43 educational resources and learning materials identified, 122 journal articles were identified in the scoping review. Of this total, 39 publications (32.0%) had previously been identified during the literature search (see **7.1**), leaving a remainder of 83 previously-unidentified publications of interest.

Theme	Search Term	Final Results (n)	Final Results (%)
1: Pharmacovigilance	“postmarketing surveillance”	3	9.1
	pharmacovigilance	29	87.9
	"adverse drug reaction report*"	1	3.0
2: LRSs	"developing countr*"	12	36.4
	"low income countr*"	2	6.1
	"middle income countr*"	5	15.2
	Africa	12	36.4
	lmic*	1	3.0
	"resource limited countr*"	1	3.0
	"resource poor countr*"	0	0
3: Resource	education*	7	21.2
	guid*	5	15.2
	learning	7	21.2
	"standard operating procedure*"	0	0.0
	SOP	0	0.0
	tutorial*	0	0.0
	template	4	12.1
	tool*	3	9.1
	video*	1	3.0
	lecture*	0	0.0
	seminar*	2	6.1
	webinar*	2	6.1
	course	2	6.1

Table 6: Relevant educational resources or learning materials returned for each search term used in the three-level search. A total of 33 relevant results were identified following the three level search. Percentage values represent the percentage of final results returned for that particular search term within its theme (eg 87.9% of the final results were identified by use of a three-level query of which the search term from theme one was ‘pharmacovigilance’). The individual three-level queries that returned the highest number of relevant results were (pharmacovigilance AND “developing countr*” AND education*) and (pharmacovigilance AND africa AND learning), both n=3.

8.4 Resource Scoping Review Discussion

Existing Pharmacovigilance Resources

A variety of pharmacovigilance resources and resource types were identified in the scoping review (**Fig. 4**). This diversity exhibits the numerous approaches taken to date to support pharmacovigilance training and education activities by relevant stakeholders around the globe. Encouragingly, the majority (88.4%) of the resources identified were accessible at no cost to the user. This demonstrates not only the existence of an accessible pool of educational pharmacovigilance resources, but a willingness to facilitate the unrestricted sharing of knowledge amongst resource developers.

The scoping review also suggested that the WHO was the major global stakeholder in pharmacovigilance resource development (the WHO had input into 23.3% of all resources identified, see **Fig. 5**). Despite this individual majority, the high number of organisations that had developed the remaining resources (n=28) showcased the abundance and diversity of institutional pharmacovigilance stakeholders around the globe. This diversity highlights the need to ensure close collaboration between these actors to focus pharmacovigilance capacity building efforts, avoid the duplication of effort (preventing the unnecessary and costly use of time and already-limited resources), and facilitate greater knowledge exchange.

83 publications of interest that had not been identified following the literature review were identified by the scoping review. This apparently large oversight of the literature review was in reality due to the relatively short time period to which the literature review was focussed (2016-2019, see **7.1**). Much of the relevant literature identified in the scoping review was published pre-2016.

As identified in the results, previous efforts have been made to collate existing pharmacovigilance resources (**Fig. 4, '**Resources Bank', n=3), however, no initiatives specifically aiming to bring

together free and open access resources dedicated to pharmacovigilance in LRSs were identified. Whilst it is acknowledged that in general, resources are likely to be of some value in the support of pharmacovigilance capacity development regardless of their scope, it seems logical that the agglomeration of resources tailored specifically to challenges facing pharmacovigilance in LRSs will be of greatest value to pharmacovigilance stakeholders, and achieve the greatest impact on pharmacovigilance capacity, in those settings.

Value of the Scoping Methodology

The identification of a range of existing pharmacovigilance resources demonstrates the importance of conducting additional knowledge synthesis activities in addition to a traditional literature review. These items represent important features in the global canon of pharmacovigilance materials that would not have been identified by searching a bibliographic database. When considered in combination with the results of the literature search, they provide a holistic overview of the pharmacovigilance landscape in LRSs, and great insight into the training and education domain. Identification of such resources is particularly valuable given the need to increase the training of HCPs and availability of training resources in order to build pharmacovigilance capacity in LRSs identified in the literature review (see **8.2**).

In addition, the findings provide insights into the terminology used to label and describe pharmacovigilance resources. This information may be of value in guiding rapid or exploratory search strategies for future research, or for those seeking to identify pharmacovigilance resources in a personal capacity. In particular, combinations of the search terms '*Pharmacovigilance*', '*Developing Countr**', '*Africa*', '*Education**' and '*Learning*' may be of greatest use when seeking to identify existing resources designed to support pharmacovigilance activities in LRSs (see **8.3**).

Limitations of the Scoping Methodology

The ability to ensure rigorous data collection was at times impeded by the software's capabilities. It was identified that some searches returned different results when repeated, even when done so within a very short time period (<5 mins). This was confirmed as a limitation of the software via contact with the software developer (personal communications, Aug 2019). It therefore cannot be conclusively determined that all potentially relevant resources were identified during the final searches.

In addition, difficulties were encountered when storing search results within the software. Search results were 'archived' to await analysis, however the software did not allow the archiving of duplicate results (the same results identified by different search terms). This also was confirmed as a limitation of the software via contact with the software developer (personal communication, Sep 2019). This meant that any resources identified and archived as a result of an earlier search, that were then also identified in a later search, would not be included in the final results of the later search. Whilst the automatic removal of duplicates may have streamlined the identification of relevant resources overall, the exclusion of such results likely impacted the total 'final results' for the later searches. It is therefore possible that several of the search terms returned a greater number of 'relevant' results (and hence were more effective search terms) than shown in **Table 6**.

At the time of usage, the software was only compatible with the macOS operating system. This may present additional challenges (and resource constraints) to those unfamiliar with this operating system, unless further updates are made to expand the operability of the software.

As described, a large number of search results were returned (n=3,725, see **Table 5**). Reviewing this volume of data was an especially time consuming process, and only a very small percentage of the results (1.2%) were found to be relevant. In addition, the relevance of many of the results were vastly outside the scope of the research; the search [*"postmarketing surveillance" AND Africa AND*

SOP] returned a manual for a 'Nokia N95 8GB Mobile Phone', and the search *["postmarketing surveillance" AND Africa AND Learning*] returned a manual for a '1998 Honda Civic'.

The only search term with a regional focus included in the final 'LRSs' theme was 'Africa' (see **Table 6**). Other regions were included in the test searches (see **Table 2**) but returned little or few final results when used in combination with other search terms, and hence were not included in the final searches for streamlining purposes. This may have introduced a regional bias into the final results, resulting in the overrepresentation of resources specifically designed to support pharmacovigilance activities in Africa. However the lack of results identified in the test searches for other regions suggests a lack of existing pharmacovigilance resources targeted to those settings.

Furthermore, the search strategy was restricted by the usage of solely English-language terms. Not only did this significantly decrease the likelihood of identifying potentially relevant non-English language results (indeed, all resources identified in the scoping review were English language resources), the regional limitations discussed above were also further compounded by restricting the source and application (without further translation) of the resources identified to Anglophone regions.

Scoping a Scoping Strategy?

To the best of the author's knowledge, this research represents the first use of DEVONagent as a fundamental component of knowledge synthesis activities in global health research. Due to the highly experimental nature of this approach, it was decided that the PRISMA-ScR guidelines would not be adopted in this incidence, to allow the pragmatic development of a novel scoping strategy, and greater freedom in the reporting of unorthodox scoping review results, namely findings from taring and educational materials, as opposed to findings from published and grey literature [67]. Moreover, the focus of 'traditional' scoping reviews on mapping available literature, was deemed to be too restrictive in scope for this review.

Nevertheless, the value in seeking to ensure the highest-possible quality of knowledge synthesis activities is clear, and many aspects of the methodological approach to this scoping review align with the approaches outlined in the PRISMA-ScR checklist. It is highly recommended that future 'resource scoping' activities looking to build on the methods described here do so by seeking to apply and report these approaches in the manner recommended by the PRISMA-ScR guidelines.

9 Conclusion

Conducting pharmacovigilance activities in LRSs is incredibly challenging. The challenges faced are interconnected and multidimensional, and there is need for improvement across all levels of the pharmacovigilance 'spectrum'.

Greater awareness of existing pharmacovigilance resources and institutional stakeholders is needed amongst pharmacovigilance stakeholders in LRSs. This will support capacity building initiatives via the facilitation of knowledge exchange, preventing the duplication of effort, and focussing the development of novel interventions to areas in which current resources are lacking.

Future efforts to improve knowledge exchange amongst pharmacovigilance stakeholders in LRSs should look to collate resources specifically designed to support pharmacovigilance activities in LRSs. Where possible, these efforts should include input and guidance from pharmacovigilance stakeholders in LRSs, to ensure their greatest possible value.

The hybrid knowledge synthesis strategy represents a valuable method for providing a holistic overview of a domain of interest when conducting experimental research. The scoping component is an arguably essential feature of capacity-building research, as existing capacity-building tools and initiatives cannot be identified using bibliographic databases. Future research should further investigate the value of specialist software to the conduction of scoping reviews, include

comparison with traditional scoping methods and alternative specialist software, and seek to apply the resource scoping methods outlined above to the PRISMA-ScR guidelines.

10 The COVID-19 Pandemic: Adapting to Circumstance

On 31st December 2019, the WHO China Country Office was informed of a cluster of cases of pneumonia of unknown etiology detected in Wuhan City, Hubei Province of China. The causative novel virus, later termed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was isolated by the Chinese authorities on 7th Jan 2020 [112]. On 11th March 2020, the disease, by then termed Coronavirus Disease 2019 (COVID-19), had spread to 114 countries/territories and was declared a pandemic by the WHO [113].

Since its emergence, the pandemic has had a devastating impact on populations and health systems worldwide, its global impact on all aspects of modern life making it the most consequential public health crisis of the 21st century to date. As of August 2022, there have been over 581 million confirmed cases of COVID-19 worldwide, including over 6.4 million deaths [114].

10.1 The COVID-19 Research Implementation and Knowledge Hub

In response to the emergence of the pandemic, TGHN launched the COVID-19 Research Implementation and Knowledge Hub (COVID Hub), in January 2020. The Hub serves as an open-access online platform designed to meet the immediate demand for support and guidance for researchers in LRSs. In order to enable rapid and efficient consensus building on the research priorities for COVID-19, TGHN adopted an action-research-led model of surveys, workshops and working groups led by researchers working in LRSs. As of August 2021, the Hub had nearly 5,000 members globally, and maintains a large user base in LRSs, with India, The Philippines, Brazil, Kenya and Uganda amongst the highest users. It has received 400,000+ visits from 195+ countries, with 20,000 COVID-19 outbreak resource downloads. The programme of workshops continues to thrive,

with 40+ workshops, and 5000+ attendees from 140+ countries. Moreover, eight working groups (with 500+ researchers from 82 countries) continue to generate solutions for specific research areas.

10.2 COVID-19 and Pharmacovigilance

The emergence of a highly-transmissible, novel infective agent spurred rapid investigation of pharmacological interventions on an unprecedented scale. Largescale collaboration, upscaled manufacturing capacity, enormous financial investment and targeted distribution of funding effected a dramatic reduction in vaccine development timelines. The first approved COVID-19 immunisation administered outside of a clinical trial setting occurred on 8th December 2020 in the UK, less than 12 months after the disease was first reported to the WHO [115]. Large scale international trials (eg the Solidarity trial, conducted across 35 countries and reaching over 14, 200 participants) were undertaken to evaluate the impact of repurposed medicines on COVID-19 mortality [116]. As of August 2022, 11 COVID-19 vaccines have been granted Emergency Use Listing (EUL) by the WHO, 41 COVID-19 vaccines have been approved for use in at least one country, and there are 222 vaccine candidates in clinical trials worldwide [117]. In addition, as per the WHO Coronavirus (COVID-19) Dashboard, over 12.4 billion vaccine doses have been administered worldwide, including two vaccines which harness novel, mRNA based vaccine technologies.

This rapid development of novel therapeutics, the use of repurposed medicines on an expanded scale, the introduction of novel vaccine technologies, and the global mass administration of novel vaccines was accompanied by an associated need for highly effective and stringent pharmacovigilance processes [118]. Safety considerations of the vaccines, driven by the mass media, have thrust medicines safety activities into the public eye. Even prior to vaccine development, the 42nd Global Advisory Committee on Vaccine Safety (GACVS) identified the need to implement vaccine safety surveillance infrastructure and capacity in all countries ahead of

COVID-19 vaccine introduction, and developed the 'COVID-19 Vaccines: Safety Surveillance Manual' in response [119]. A report from the ISoP Executive Committee on the organisation's role during the pandemic identified that 'monitoring the safety of medicines is an obvious top priority', and acknowledged that whilst the pandemic presents additional challenges to medicines safety monitoring, the increased attention on pharmacovigilance offers a valuable opportunity to strengthen and harmonise safety activities [120].

10.3 COVID-19 and Pharmacovigilance in LRSs

Given the impact that the COVID-19 pandemic is having upon health systems globally, it is essential to ensure that pharmacovigilance systems in LRSs have the capacity to address both the exacerbated pre-existing (see **8.2**) and novel challenges that they now face. In Feb 2021, a priority setting exercise coordinated by the Africa Centres for Disease Control and Prevention (Africa CDC), WHO Regional Office for Africa (WHO-AFRO) and African Academy of Sciences (AAS) identified both the facilitation of COVID-19 drug and vaccine safety studies, and the need to capture data on drug and vaccine side effects, as research priorities for COVID-19 in Africa [121]. Following the vaccine introduction, vaccine safety concerns have been identified as a barrier to COVID-19 vaccination in LMICs [122]. Notwithstanding the obvious need to strengthen pharmacovigilance capacity during the pandemic, concerns have been raised about the ability of LRSs to augment their existing pharmacovigilance processes; prior to the pandemic, only 27% of countries in Southeast Asia and 21% of countries in Africa met the WHO threshold for a functional vaccine pharmacovigilance reporting system [123]. It is clear that there is an immediate need to strengthen medicines safety activities in LRSs to prevent medicines-related harm during the pandemic, and maintain public trust in healthcare systems.

Part II: Methods

III Study Design

11 Theoretical Approaches

The multidimensional, community-driven, capacity-building nature of this research necessitated the adoption of multiple, complimentary methodological approaches. This project applied an action research, mixed methods approach, and utilised a CoP model to guide community development. In this chapter, each of these methodological components will be introduced, and their application to this research discussed in detail.

11.1 Mixed Methods

Mixed methods research can be defined broadly as 'the combination of quantitative and qualitative research' [124]. The advantages of mixed method research have been discussed at length in methodology research literature. It has been proposed that, in contrast to quantitative or qualitative paradigms adopted separately, mixed methods research increases the validity of research findings, offers a broader and holistic understanding of the phenomenon under investigation, and provides the opportunity to take advantage of the strengths of each individual approach collectively [125, 126].

A flexible mixed methods design was applied to the methodological strategy. Building on Creswell and Plano Clark's four design framework, this approach can best be described as an 'adaptive embedded design' [124]. Quantitative and qualitative data was collected and analysed concurrently at each stage of the research, and then compared and interpreted collectively. However, the emphasis on either quantitative or qualitative components varied according to aims of the methodological component. Traditional triangulation design was considered unsuitable due to the general equal emphasis on both data forms at the interpretation stage (see **Fig. 6**). Given the lack of pre-determined data-collection methods, and the uncertain nature of the project direction and

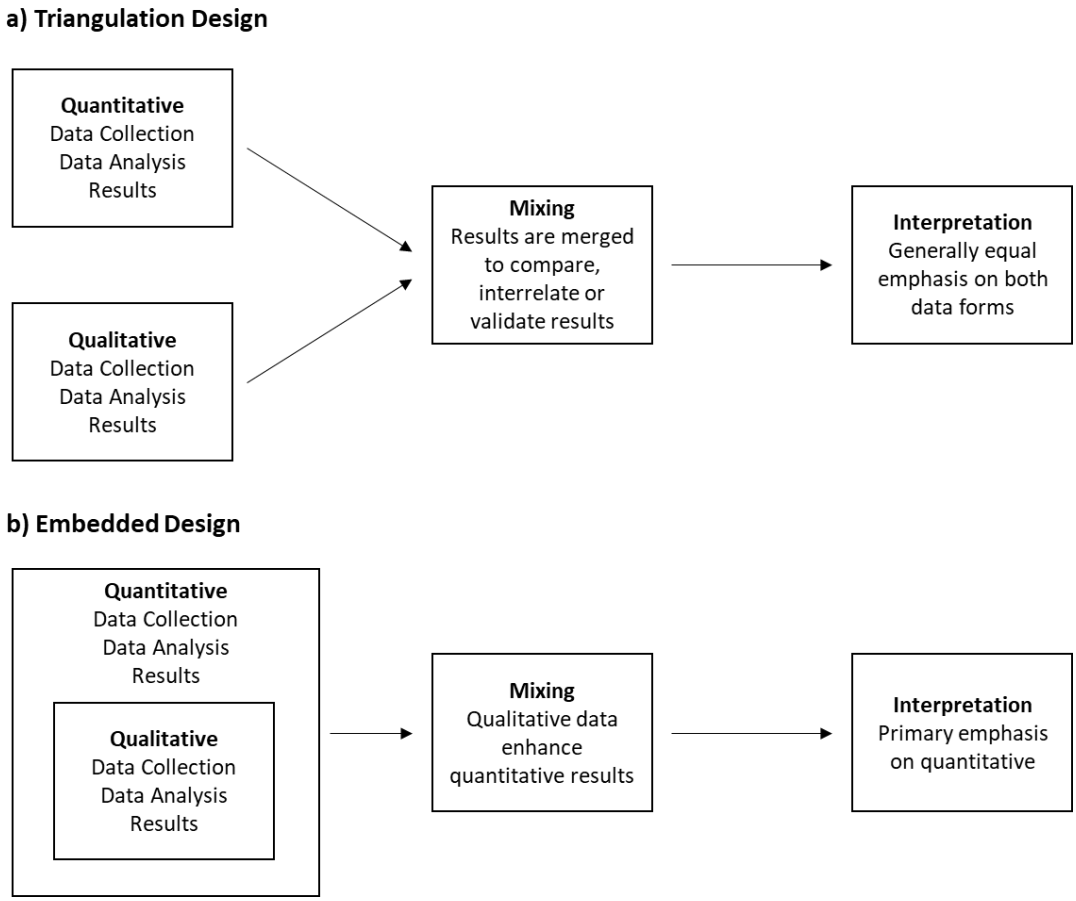


Figure 6: Triangulation vs Embedded mixed methods design. Adapted from Creswell and Plano Clark's four design framework (2007). The embedded design example (b) demonstrates qualitative data embedded in a quantitative framework, however the reverse is also possible. The primary data type (in the above example, quantitative) is determined in advance of data collection and is uniform throughout the research.

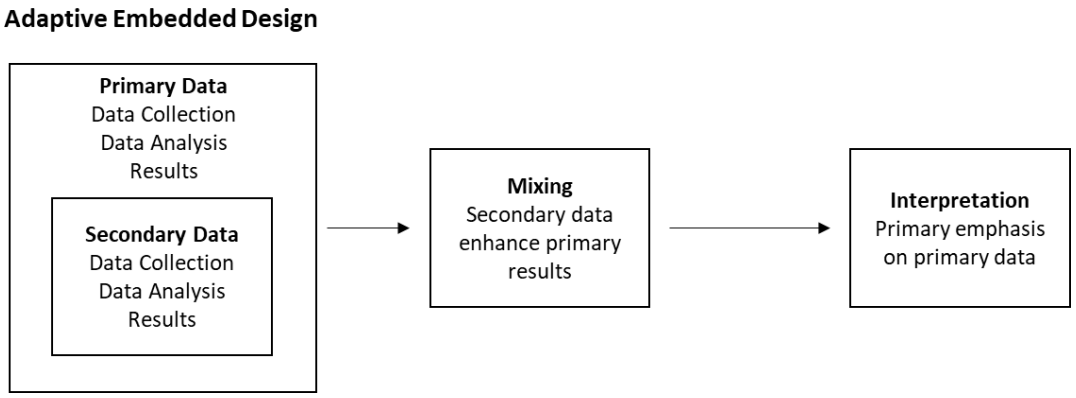


Figure 7: Adaptive Embedded Design Framework. The primary and secondary data types (either qualitative or quantitative) are unknown in advance and are dependent upon the data-collection method involved. The data type classifications are not fixed throughout the research, and vary according to the data-collection methods being conducted.

outcomes, equal emphasis on quantitative and qualitative data during interpretation could not be guaranteed. An embedded design allowing for flexibility in the emphasis on data type was therefore adopted (see **Fig. 7**).

11.2 Action Research

The overall methodological approach of this research was based on a conceptual framework of action research. This was primarily due to the immediate examination of research in context afforded by action research. A participatory community approach ('third person' or 'emancipatory') was taken to ensure that the research would be led by, and be of the highest possible relevance and value to, the participants. Given the unknowns that surrounded the additional methodological considerations (eg community attitudes towards CoP involvement), and the turbulent nature of global events at the time of the research (ie the COVID-19 Pandemic), the flexibility and adaptability of the action research approach was also considered to be a valuable advantage. In addition, the participatory nature of this approach and the shared theoretical origins with CoP theory (see **11.3**), were considered to make action research and CoP theory complementary methodologies to apply to this work.

11.3 Overview of Action Research

The term 'Action Research' was first coined circa 1944 by German-American psychologist Kurt Lewin (1890-1952), and was discussed at length in his 1946 paper 'Action Research and Minority Problems' [127]. Lewin was the first to propose the four stage 'Action Research Cycle', in which researchers plan, act, observe, and reflect in an iterative cycle (see **Fig. 8**). The repeated continuation of this cycle towards the resolution of a problem, or in the direction of continual improvement, has been termed the 'Action Research Spiral' or 'Lewinian Spiral'.

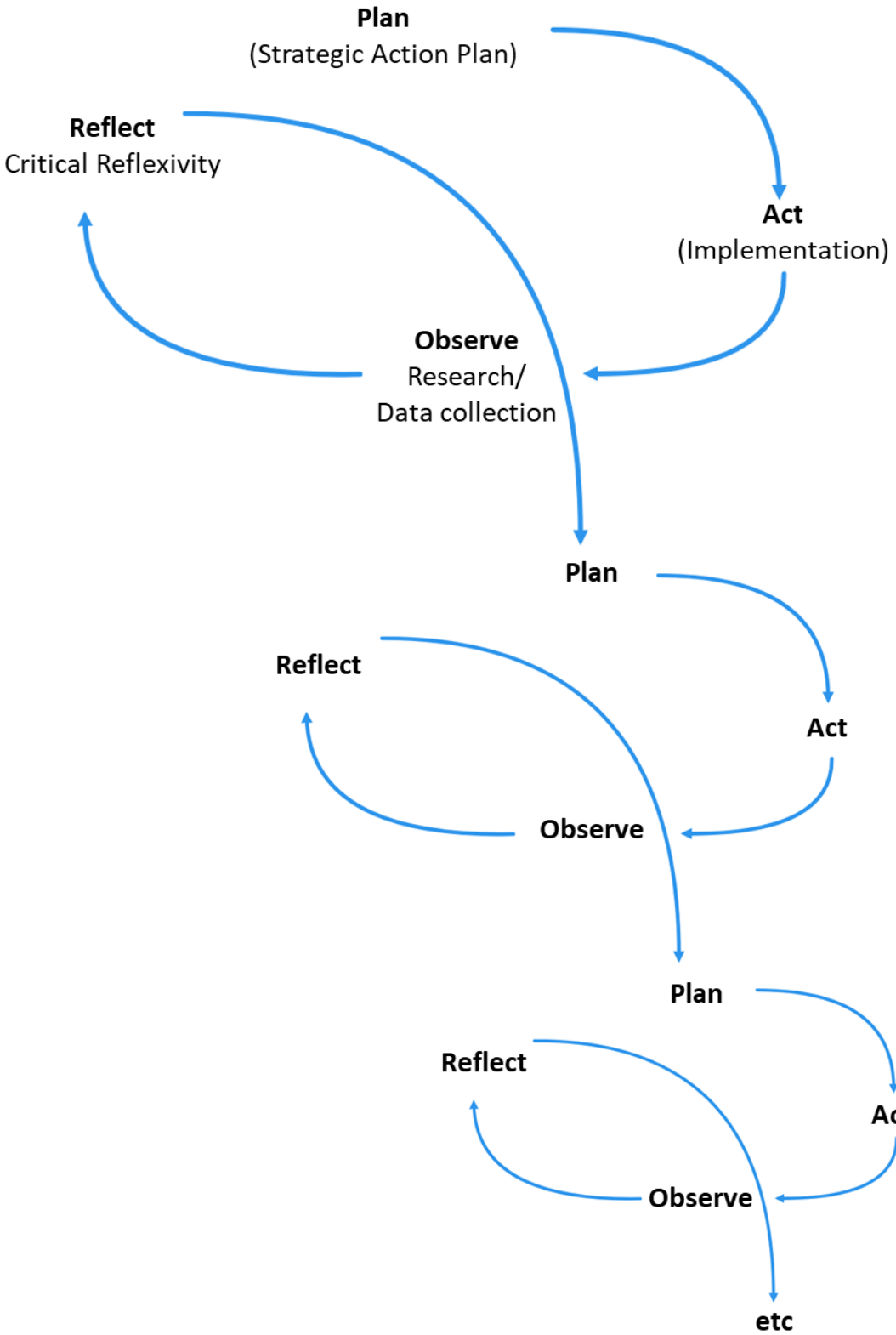


Figure 8: The 'Action Research' or 'Lewinian' Spiral. The iterative cycle of Planning, Action, Observation and Reflection is demonstrated. Modelled on Figure 1.3, 'Action Research: Rethinking Lewin' Dickens and Watkins, 1999 [128].

Action research is rooted in the same philosophical framework as CoP theory. Lewin's work was strongly influenced by the earlier work of American psychologist, educational reformer and pragmatist John Dewey (1859-1952). In his numerous works on democracy and education, Dewey advocated that education was an inherently social process, that learners should be the foremost concern to teachers and not adherence to a curriculum, and that knowledge and action are inseparable.

Lewin has been labelled 'The Founder of Social Psychology' and is known primarily for his work on Group Dynamics and Organizational Development. Indeed, components of CoP theory can be seen in Lewin's earlier 'T-Group' model.

A myriad of definitions and interpretations of action research have emerged since the term's inception, each seeking to build on Lewin's initial theory. Despite this variance, it is largely agreed that action research follows Lewin's iterative four stage cycle, has a practical, problem solving emphasis, and is undertaken to 'understand, evaluate and change' [129]. In addition, it is considered to describe a methodological 'family', focussed on establishing collaborative relationships, and creating 'communicative spaces', and is an organic, pragmatic process which cannot be predetermined but '*changes and develops as those engaged deepen their understanding of the issues to be addressed and develop their capacity as co-inquirers both individually and collectively*' [130]. Action research principles have been examined in a number of fields, including education, sociology, business, and healthcare [131-134].

There are a number of theoretical approaches to action research, including co-operative inquiry, participatory action research (PAR), and action science, each of which vary in their scope and theoretical underpinning. The varying approaches have been categorised using a point-of-view metaphor, Reason and Torbet's 'First-, second-, and third-person dimensions of inquiry'; 'First person' approaches can be described as those that focus on the individual, 'Second person' those that engage in tight-knit, face-to-face groups, and 'third person' approaches being those that aim

to create much larger communities of inquiry, who may not be known to one another due to, for example, geographic dispersal [135, 136]. Similar classifications have been proposed; Carr and Kemmis' three types of action research, 'technical', 'practical' and 'emancipatory' for example has some similarities with Reason and Torbet's approach [137].

An action research approach has a number of advantages. Most crucially, it allows the immediate examination of research in context. Research is therefore immersed in its relevant setting and is not conducted from a purely external, theoretical perspective, which serves to enhance the relevance and applicability of its findings [138]. The flexibility of the methodological framework also offers numerous advantages, including the ability to easily modify research to circumstance and the opportunity for theory to emerge from research, as opposed to a rigid reliance on a predetermined theory [139].

Action research is not without its challenges. In capacity building research, it is an attractive but complex concept, with many nuanced and abstract interpretations. A thorough understanding of its theoretical principles, and the appropriate skills to conduct action research, may be lacking amongst both researchers and participants [138]. Action research practices are also often identified as time consuming and personally demanding for researchers. Collaborating participants must be identified, personal relationships must be established, project resources must be developed and new skills must be learnt and researchers may be required to take on many roles traditionally considered to be additional to the remit of a researcher (eg Project Manager) [140]. In addition, the organic nature of action research prevents the determination of precise research timelines. Researchers planning to adopt an action research-based methodology should be well aware of these limitations and make efforts to reduce their impact accordingly.

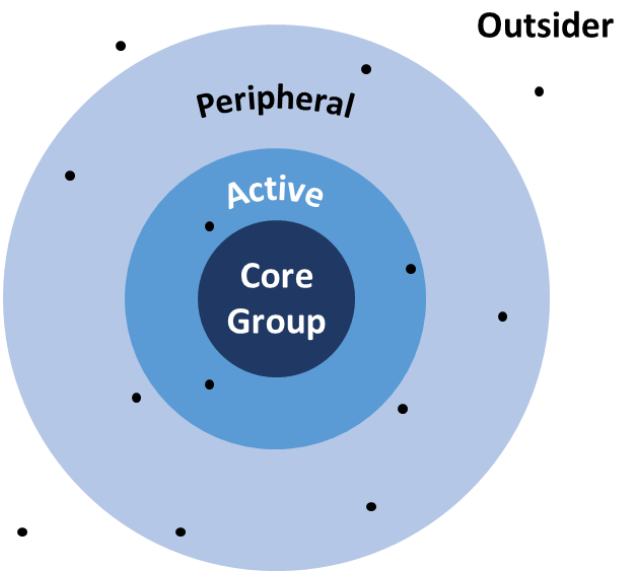


Figure 9: Levels of CoP participation. Modelled on Figure 3.1, 'Cultivating Communities of Practice: A Guide to Managing Knowledge', Wenger et al, 2002 [47].

11.4 Application of Community of Practice Theory

A CoP model was used to guide the community development strategy. Wenger et al's '*Cultivating Communities of Practice: A Guide to Managing Knowledge*' was used as the primary reference for guiding community development, although a range of additional references and perspectives on the CoP approach were also consulted [47].

The constituent elements of the CoP were defined prior to participant recruitment, according to the aims of this thesis (see 5). Given the diverse scope of pharmacovigilance and its activities, the international focus of this research, the desire to engage pharmacovigilance stakeholders across the entire spectrum of pharmacovigilance activities, and the intention to adopt a flexible, indefinite action research approach, a broad approach to CoP delineation was taken, as outlined by Hodkinson and Hodkinson [48]. This was reflected in the broad nature of the CoP element definitions (see **Fig. 2**).

Different levels of community participation were invited throughout community development, as advised by Wenger et al (see **Fig. 9**). An example of this participatory strata can be found in the establishment of Working Group Coordinating Groups (see **20.2**).

12 Research Platforms

GPV was used as a platform for communication and dissemination of results/outputs. This included the use of the GPV communication channels (mail lists and social media accounts). The platform underwent continuous development in response to the research progression and findings.

As the umbrella network, TGHN communication channels were also adopted to disseminate project information. It was envisaged that GPVs place within the wider TGHN platform, would allow crosscutting interactions to be made with other member hubs and CoPs when relevant. Pertinent information was disseminated on other TGHN member hubs when necessary, and in agreement with the respective hub coordinators.

13 Contextualisation

It has been acknowledged that careful consideration of the terminology used to describe the research context is important in global health research (see **3**). In this work, 'LRS' was used at the project level to contextualise the settings to which this overall body of work is applicable too, whilst 'LMIC' was used to contextualise individual research activities at interfaces with participants (eg survey, workshop and working groups). The reasoning for this was as follows:

- Whilst still an umbrella term, the term 'LRS' does not emphasise economic factors as a determinate of healthcare capacity, nor does it not apply geographic boundaries to the research context, which allows for a more reflexive consideration of target regions and

healthcare capacity determinants.

- Whilst acknowledging the connotations of power imbalance inherent within hierarchical classifications ('Low'), the inclusion of this definitive categorisation in 'Low Resource Setting' provides a more focused context than 'Resource-Constrained/Limited Setting', and so centres the focus of this research to settings with the greatest capacity inequities.

- Whilst acknowledging the limitations of the term 'LMIC' this term was employed at any interface with participants (as opposed to 'LRS') for operational simplicity. It was assumed that participants were likely to have a greater familiarity with the term 'LMIC' than 'LRS', and thus, the use of the term 'LMIC' would provide better contextualisation of the research at the participant level. In addition, it was assumed that the rigid but simple economic definition of an LMIC, and the ease of accessibility of The World Bank Economic Classifications, offered the ability for participants to self-identify the relevance of the research to their setting, reducing the potential for confusion stemming from the use of more abstract terms (eg 'LRS').

- Whilst acknowledging that the terms 'LRS' and 'LMIC' are not interchangeable, it is proposed that there is some degree of generalisation between the LMIC contextualisation at the participant level, and the LRS contextualisation at the project level. Thus, findings contextualised in LMICs will be considered applicable to an LRS context, when exploring the wider implications and outcomes of this project. The limitations of this generalisation will be discussed.

14 Population of Interest and Participant Recruitment

The population of interest was defined as follows:

- Those with an involvement in pharmacovigilance in LRSs.

The population of interest was communicated to potential participants at all stages of this research. As discussed above (see **13**), the term LMIC was used to contextualise this research at interfaces with participants, and so in participant communications the population of interest was described as 'Those with an involvement in pharmacovigilance in *LMICs*'.

Participants were recruited from the membership of TGHN. Recruitment was primarily targeted at the membership of GPV, although participation was open to the entire membership of TGHN. Interested or relevant persons who were not existing members of TGHN, identified via personal communications, referral via CoP members or via TGHN/GPV's social media channels, were invited to register as TGHN members prior to participation.

15 Ethical Approval

This research was reviewed and approved by the Oxford Tropical Research and Ethics Committee (OxTREC), reference: OxTREC 541-18.

16 Overview of Methodological Components

Due to the adoption of the iterative, reflective action research approach, the precise methods by which the aims of this thesis were sought to be achieved were not wholly determined in advance. The exception to this approach is the survey (and by extension, the validation process, although this process itself was initiated following reflection upon initial survey development). This lack of predetermination was deemed crucial to ensuring the informed but organic development of research activities specifically tailored by the outcomes of the previous research stage, and to the greatest immediate needs and value of the CoP members.

Below, and in-depth discussion of each methodological component of this research is provided. A discussion on the results and outcomes of each of these stages can be found in the subsequent chapters. It is reiterated that whilst these stages are presented here in advance of individual discussions and reflections on each research cycle, decisions regarding the choice of methodology, and the exact research objectives, for each subsequent research cycle following the survey, were made only following reflection upon the previous research cycle. As such, the decision to conduct a workshop as part of consensus building activities was only made following reflection upon the outcomes of the survey, and the decisions guiding the formation of working groups were only made following reflection upon the outcomes of the workshop.

An overview of the methodological components of this research, highlighting specific research activities within iterative action research approach, is shown in **Fig. 10.**

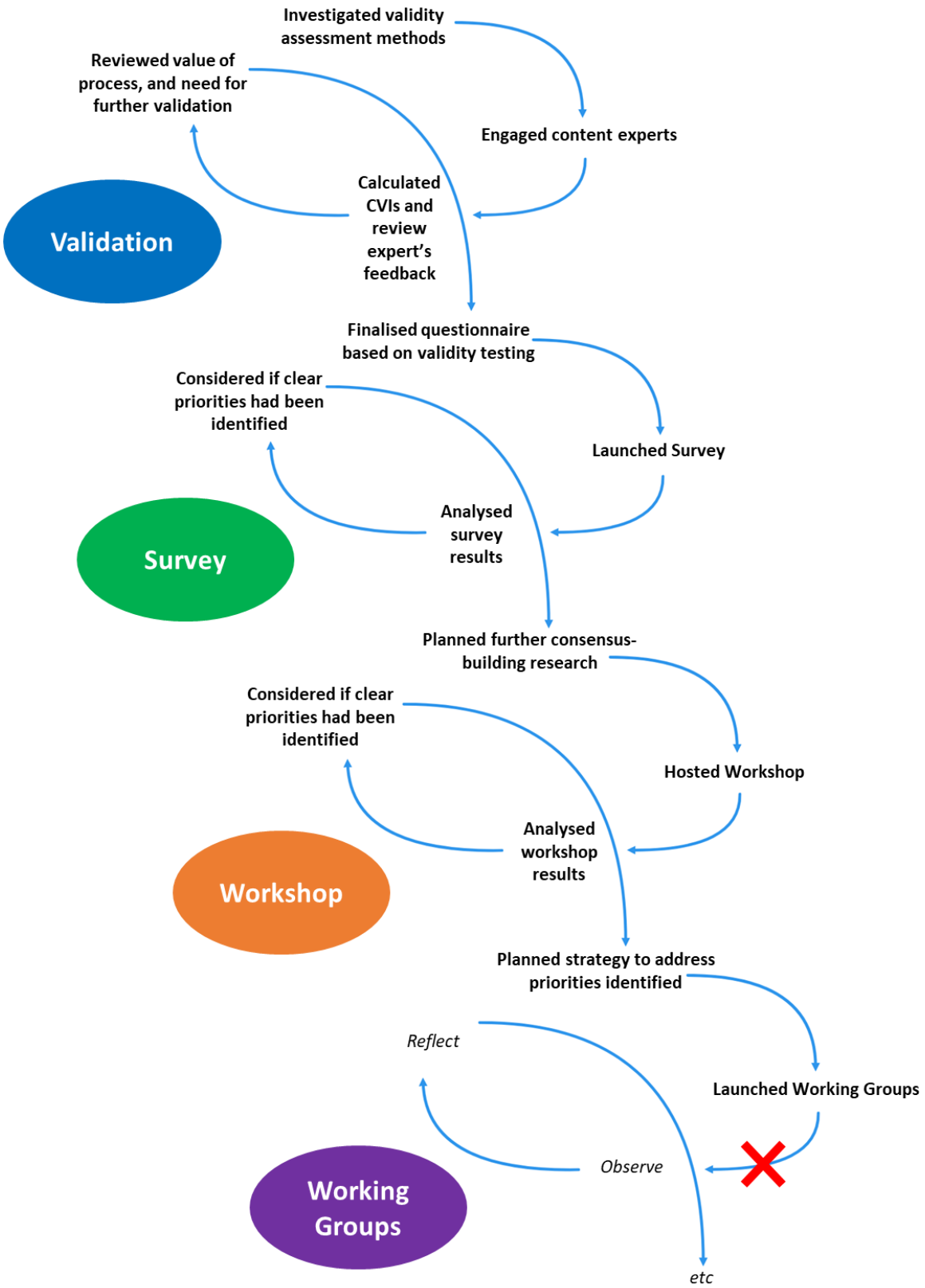


Figure 10: The stages of this research within the action research spiral. Clockwise research categories are 'Plan', 'Act', 'Observe', 'Reflect', see **Fig. 8**). Examples provided at each stage may only represent one of a number of actions that apply to that point in the research cycle. For example, 'Act' in the validation cycle also included the development of the validation questionnaire and debriefing documents. The red cross marks the final point in the action research spiral of this project.

17 Consensus Building Methods: Survey Validation

A cross-sectional survey was designed to identify pharmacovigilance knowledge gaps amongst pharmacovigilance stakeholders in LMICs. During the initial stages of development (pre-emergence of the COVID-19 pandemic, see **10**), the intent was for the survey to identify knowledge gaps in specific relation to pharmacovigilance in Africa. However, following the emergence of the pandemic during survey development, and the abrupt and enormous health systems pressures that resulted it was decided to pivot the project's aims to address the obvious challenges presented by the pandemic. The survey aims were therefore adapted, to identify and prioritise pharmacovigilance knowledge gaps in LMICs, with specific relation to the COVID-19 pandemic

17.1 Preliminary Survey Design

An online questionnaire was designed using Microsoft Word and the Jisc Online Surveys tool (see **Appendix 8** for the final questionnaire) [141]. Bryman's '*Social Research Methods*' served as the primary reference during the design process [142]. Additional survey-design literature was consulted when necessary. The questionnaire was written in English and was not translated to any other languages.

Item generation

Questions which sought to assess the survey's primary aim, '*To identify and prioritise pharmacovigilance knowledge gaps in LMICs with specific relation to the COVID-19 pandemic*' (hereafter referred to as 'knowledge gap questions', Q2-Q6 in the final survey) were developed following the literature review (see **7.1**), attendance of relevant online webinar(s)/workshop(s) (eg WHO Global Consultations on R&D Agenda for COVID Vaccines) and personal communications with pharmacovigilance experts.

Questions which sought to address the additional aims were developed pragmatically, to gather an appropriate level of data to address each aim.

Question Design

The questionnaire included both open- and closed-ended questions. Closed-ended questions included both multiple and forced-choice responses, depending upon the question's aim. A range of question types were included:

- **Questions about knowledge**: A question was included to assess respondent's knowledge of the definition of pharmacovigilance (Q1 in final survey) This question was included for two reasons; Firstly, to act as a filter for participants lacking the necessary baseline knowledge to provide meaningful data, by both the inclusion of pharmacovigilance-related terms in the response options (allowing potential respondents unfamiliar with the field the opportunity to self-selectively decline survey participation) and also by allowing the researchers to identify and remove responses of participants who demonstrated a widely mistaken understanding of pharmacovigilance; Secondly, to assess the participants awareness of the expanded scope of the field of pharmacovigilance. The question was design using the WHO definition of pharmacovigilance including a consideration of the science's expanded scope and aims [143].

- **Questions about attitudes**: Knowledge gap questions were assessed using grouped 5-point Likert items. Items were grouped according to their overarching focus. Definitive groupings were determined following survey validation (see **25**). Each pharmacovigilance priority identified during item generation was preceded with the question frame '*I need to know more about…',* for example *'I need to know more about how to report Adverse Events Following Immunisation'* (AEFIs). Using the 5-point scale ('Strongly Disagree',

'Somewhat Disagree', 'Neither Agree nor Disagree', 'Somewhat Agree' and 'Strongly Agree'), participants were asked to indicate their level of agreement as to whether they thought that they needed to know more about that topic

- **Personal factual questions**: These questions were designed to gather demographic data and data on the usage of GPV (Q9, Q11, Q13-16 in final survey) To avoid ambiguity, in questions assessing frequency (eg Q11.a, '*In the past 12 months, how frequently have you engaged in pharmacovigilance activities?*'), specific frequencies were provided ('More than once a week', 'Once a week', '2 or 3 times a month' etc). It was also ensured that time periods did not overlap.

Survey Structure

Knowledge Gap questions were grouped into tables to ensure clear presentation of a large number of similar questions, and to reduce the overall questionnaire length by making efficient use of space. Response options were arranged horizontally to accommodate this format.

Addition Likert-type item (eg Q12) responses were arranged vertically, as advised in survey design literature, to ensure obvious visual distinction between response options, and to clearly distinguish question from answer [142].

Following experimentation with randomisation, it was decided to prioritise 'question flow' over randomisation when determining question order. This was to ensure maximum clarity and ease of response for participants when completing the questionnaire, in particular the question-dense Knowledge Gap section. In addition, true randomisation (individual randomisation for each participant) was not possible using the Jisc tool.

Demographic questions (years of experience, job role, institution, country etc) were deliberately placed at the end of the questionnaire. This was to reduce the likelihood of non-completion by less

experienced participants, who may have been discouraged from completing the questionnaire if they had seen response options for high-levels of experience and highly-qualified job roles at the beginning of the survey.

Additional amendments and structural considerations were made following the survey validation process (see **25**), when necessary.

17.2 Survey Validation Theoretical Background

Before a new tool can be launched, it must be tested to ensure that it is relevant to its field, and will effectively fulfil its intended purpose. This concept is termed validity, and whilst precise definitions of validity vary in the literature, it can broadly be defined as the extent to which a tool 'elicits an accurate description of its target concepts', or, 'the extent to which the instrument measures what it is intended to measure' [144, 145].

With respect to the context of the survey, validity describes the extent to which the questionnaire provides a useful indication of pharmacovigilance priorities in LMICs during the COVID-19 pandemic.

17.3 Types of Validity

There have been numerous attempts to fractionate the concept of validity according to method, depth of inquiry, and the intended purpose of the measurement tool. Indeed, no less than 35 terms have been identified to connote different types of validity [145].In general, researchers accept four different types of validity, although there may be disagreement on the value of each of these concepts, the distinct forms that they take, and whether overlaps exist between each type. In addition, further divisions and sub-categories may be proposed within these four overarching categories. These are detailed in **Table 7**.

Type of Validity	Description	Advantages	Disadvantages
Face Validity	The tool appears to be a reasonable way to estimate the targeted construct – it 'looks good at face value'	Straightforward and relatively quick to assess Widely used validity testing measure in LRSs	Very subjective May be reliant upon assumptions Has been considered a component of Content Validity, rather than a stand-alone validity type
Content Validity	The degree to which the instrument fully assesses or measures the target concept Describes whether the items of a measure are representative of the domain of interest	Useful measure of validity when investigating complex, multidimensional concepts Involves consultation of a panel of experts who can offer valuable insights on tool development and wider research plans	Also relies on subjective opinions Scope can overlap with Face Validity and Construct Validity
Criterion Validity	A measure of a tool's agreement with, or empirical association with, an external criterion that is considered the gold standard Sub-types included Concurrent and Predictive Validity	Relatively simple, statistically-based measure to calculate	Comparative standards may not be available or easy to establish
Construct Validity	The degree to which a tool is truly measuring the construct it was designed to measure Involves theoretical consideration of how a tool can be associated with alternative instruments and measures designed to assess the same construct Sub-types include Convergent and Discriminant Validity	A very rigorous measure of validity Has been described as 'the most valuable form of validity'	Difficult to measure/quantify Abstract concept to communicate Comparative measures may not be available Scope can overlap with Content Validity

Table 7: An overview of the four main types of validity. Precise definitions of each validity type can vary in the literature. The above information was guided by Lynn 1986, Jensen 2003, Bellamy 2015, Bolarinwa 2015, and Ruel et al 2016 [144-148].

17.4 Which to Assess?

Following a consideration of the factors in **Table 7** and the aims of the survey (see **23**), it was decided to measure the validity of the survey questionnaire by testing its content and face validity. This was for the following reasons:

- Criterion Validity could not be measured in this context; Due to the subjective nature of the concept of knowledge gaps, no gold standard can exist to measure this phenomenon.

- Construct validity could not be rigorously tested; Due to the focus of this research on a novel disease, the researchers were not aware of any comparative existing tools seeking to assess knowledge gaps in relation to the pharmacovigilance of COVID-19 vaccines in LRSs. In addition, the extensively rigorous process of assessing construct validity was deemed to be unnecessarily time-consuming, considering the need to identify the immediate challenges facing pharmacovigilance in LRSs.

- The multifactorial scope of pharmacovigilance makes Content Validity an important factor to demonstrate (see **2**).

- The GPV membership provides an existing and accessible pool of pharmacovigilance experts for the assessment of Content Validity.

- Overlaps in the theoretical underpinnings of face and content validity make them complementary forms of validity to assess concurrently.

- Weaknesses in the subjective aspects of each validity measurement are strengthened by the concurrent assessment of an additional type of validity.

- Face validity is straightforward and rapid to assess.

17.5 Methods of Determining Content Validity

There have been many methods suggested in the literature for assessing the content validity of a novel tool, many involving the consultation of a panel of experts. These include the Index of Item-Objective Congruence, Average Congruency Percentage (ACP), the use of coefficient alpha, modified Kappa statistic, and the Content Validity Ratio [149-152]. The most commonly adopted by far in healthcare research however, is the Content Validity Index/Indices (CVI)* [145, 151, 153]. The CVI was first discussed in-depth by educators Hambleton et al and Martuza in the 1970s and has since been examined and critiqued extensively in the literature [149, 154]. In particular, the CVI has been applied extensively in nursing research, although recent examples exist of its adoption in pharmacovigilance literature [151, 155, 156].

In their appraisal of the CVI, Polit et al made a detailed comparison of the various methods for determining inter-rater agreement. In their discussion of the criteria for selecting such a method, they identified that in comparison to other methods, the CVI provides both item and overall tool validity information, whilst also being straightforward to communicate and compute. In addition, the CVI specifically demonstrates the extent to which there is expert consensus about the relevance or items or tools to the target construct, as opposed to other methods which indicate the extent of any type of agreement, whether it be positive or negative [153].

17.6 The Content Validity Index

The CVI is an expert-driven rating system used to assess the content validity of a tool. The methodology can be used to assess validity at both the individual item level, termed Item-Level Content Validity Indices (I-CVI), or overall instrument level, termed Scale-Level Content Validity

*Sometimes referred to as the 'Index of Content Validity'.

Indices (S-CVI) [147, 151, 153]. Having built on Lynn's earlier work, the standardised use of the term 'scale' in the latter indices was proposed by Polit and Beck, who were primarily concerned with scale development [145, 151, 153]. Nevertheless, it should be clarified that the S-CVI is not specific to scales, and can be used in the content validity assessment of other research tools and instruments [145].

The CVI relies on a panel of experts (or 'validators') who assess a tool and its items according to their relevance to the target domain. It is calculated using an ordinal 4-point Likert scale, in which 1 indicates the lowest degree of validity and 4 indicates the highest. I-CVI is determined by the proportion of experts who rate an item as valid to some degree (a rating of 3 or 4) and S-CVI is determined by the proportion of total items judged content valid [151-153]. Whilst 3 and 5 point scales have been utilised to calculate the CVI in the past, a 4 point scale is considered preferable as it precludes an ambivalent 'middle rating' point. [145, 151].

Whilst the methodology for calculating I-CVI is uniform, there are discrepancies in the literature as to how S-CVI is defined, and therefore calculated [151]. It is important for researchers to understand the differences in these definitions and to report which method was used, as they can yield significantly different results for an S-CVI. The first S-CVI definition is 'the proportion of items on an instrument that achieved a rating of 3 or 4 by *all* the content experts' and has been termed S-CVI/UA (Universal Agreement). The second concerns the *average* proportion of items on an instrument that achieved a rating of 3 or 4 across the content experts, termed S-CVI/Ave (Average) [151-153]. In both incidences, the 4-point scale is dichotomised; items are consider according to whether they were rated 1 or 2 (not valid), *or* 3 or 4 (valid).Whilst there are multiple methods of computation for S-

CVI/Ave, all will yield the same results, and Polit and Beck argue that 'it is best to conceptualize the S-CVI/Ave as the average I-CVI value because this puts the focus on average item quality rather than on average performance by the experts.' [151].

S-CVI/Ave is a more liberal approach, as S-CVI/UA requires universal agreement amongst validators. This becomes increasingly unlikely as more validators become involved, with the probability of all validators agreeing on relevance being 0.5^N, where *N* is the total number of validators [151, 153].

17.7 Selection of Content Experts

There is no predominant consensus in the literature as to how experts should be selected for a CVI assessment, and as to what qualifies a 'content expert'. Approaches include selection based upon attainment of a professional certification, clinical expertise, history of publication, involvement in research, and level of experience (eg >10 years) in the domain of interest [144, 157-161]. Many authors reference such a criteria proposed in the nursing literature by Grant and Davis, although Polit et al later summarised that content experts 'should be selected with care, using well-defined criteria' [153, 161]. Indeed, in one of the earliest descriptions of the CVI, Martuza simply states that 'content validity judgements require subject matter expertise' [149].

In addition to professional qualifications and expertise, it is important to note that 'lay' experience and environment can also be used to qualify experts. For example, in one study that sought to develop a questionnaire to assess neuropathic pain, patients with neuropathic pain were included as content experts during validity testing [144]. A qualitative meta-analysis of procedures adopted by psychological and educational test developers to ensure content validity found that the vast majority (43.1%) of 'experts' consulted across 46 projects were undergraduate students [162]. This demonstrates that many researchers do not consider a university degree, published work or years of experience 'in the field' measures of what makes an 'expert'.

The pragmatic selection of experts can increase the likelihood of ensuring that every aspect of a domain is covered. In healthcare studies, investigators often seek to create a multi-disciplinary panel, with a range of backgrounds and professions [159, 163]. Grant and Davis also postulated

that, if plausible, selecting experts from different geographic regions increases the chance of identifying colloquial terms and phrasing during tool design [161].

It can be seen that there is no clear criteria for the selection of experts for CVI assessment. It is agreed that a 'rigorous criteria' for expert selection should be defined before contact with potential panel members begins, but this criteria will be idiosyncratic to each project and be dependent upon factors including the research aims, the field of interest, funding, time scale and logistics. Similar conclusions have also been made in other qualitative research methods [164].

The number of experts necessary to determine content validity has also been discussed at length in the literature. Examples range from as little as 2, to more than 20 (one qualitative meta-analysis found an average of 27 experts were consulted over 46 studies/projects) [149, 152, 158, 159, 161-163]. In healthcare research however, most researchers tend towards the more conservative end of the range. Most recent publications reference Lynn's work, which postulates that a minimum of three experts is needed to determine content validity (any fewer would be statistically unjustifiable due to the high likely of chance agreement between two experts) and that a maximum of 10 would probably be sufficient (assumedly due to the extremely small possibility of chance agreement between a panel of this number). Lynn suggested that when possible, a minimum of five experts is the ideal number to control for chance agreement [145, 153, 165]. Building on Lynn's work, Polit et al. recommended that (for a first round of validity assessment), a panel at the larger end of Lynn's recommendation of between 8-12 members is ideal [153]. Ultimately, whilst these recommendations provide a useful target for researchers when seeking content experts (and there is universal agreement that a minimum of three experts is necessary), Lynn's comments on expert selection continue to ring true; expert selection 'depends on how many accessible and agreeable persons the instrument developer and user can identify' [145].

17.8 Engaging Content Experts

When consulting a panel of experts for instrument review, it is important that the experts are well-informed of the instrument and overall study aims, concepts and methodologies. Investigators should ensure that content validators have an awareness of the study hypotheses and general goals for instrument usage, as well as a good understanding of the terminology used in the instrument. In addition, and pertinent to the CVI, there is a need to ensure clarity in how experts are expected to effectuate content validation. Unclear validation instructions are likely to affect expert's conceptualisation of the target domain and hence the validity of their responses [160, 161]

To address these concerns, Grant and Davis recommended the distribution of accompanying items to the validation tools:

- **Cover Letter** – used to solicit panel members participations. This should state why the investigator was chosen as a content expert, and underpin the purpose of the instrument and study outcomes, as well as include more general information about what will be expected of the expert.
- **Content Domain and Element Definitions** – Allows the experts to compare each instrument item to the target domain, and can be used to clearly indicate the meaning of the desired elements.
- **Instructions for Content Experts** – Specific instructions as to how the validation tool should be completed. Key elements of the tool should be highlighted [161].

17.9 Rounds of Validation

If, following expert review and calculation of an instrument's S-CVI, an acceptable level of agreement amongst experts has not been reached, further action is necessary. Firstly I-CVIs should be reviewed. Items with an unacceptable I-CVI can either be deemed irrelevant and removed from the tool, or amended for further review. If the removal of irrelevant items still does not raise the S-

CVI to an acceptable level, or if the decision is made to amend low-rated items rather than remove them, a second round of validation is necessary.

When undergoing a repeated content validity assessment, it is recommended that a smaller panel of validators is used than in the first round. Polit et al suggests that, whilst 8-12 validators are recommended for the first round, 3-5 should be sufficient for the second. In addition, it has been recommended that second round experts are drawn from the same pool as the first, so that data from the first round can be used to select experts for the second. This can allow the selective elimination of experts who were consistently harsh or lenient in their rating, and through the collection of qualitative feedback, identify experts with the strongest content capabilities and commitment to the project. Lynn suggests that if the same experts are used in repeated assessment of an instrument, a 10-14 day period between assessments should be an adequate time interval [145, 153].

It is possible that following a second round review, the S-CVI may still not have reached an acceptable level. Further rounds of validation may then be necessary but this is likely to depend upon an investigator's timescale and funding.

17.10 An Acceptable Level of Validity

Many authors have sought to determine an 'acceptable' or 'standard' CVI, that is, a CVI value which indicates an acceptable level of agreement* as to whether an item or tool is deemed relevant to its domain. Historically, there have been different values proposed for this acceptable level of agreement and different methods suggested for its interpretation. Much of the early literature suggests a standard minimum value of 0.80 or above [149, 151, 157, 160]. This largely appears to be rooted in Martuza's early advice that a truly acceptable level of agreement depends upon the researcher's circumstances, and can only be determined once the investigator has experience using

* The term 'interrater agreement' has been used to describe this concept [149].

CVI, suggesting 'until that experience has been gained, [interrater agreement] greater than or equal to 0.80… should be [a] useful guide' [149]. Some authors have gone on to recommend approaches for items that fall below this acceptable level of agreement. A recent overview of the content validity process suggests that if an I-CVI falls between 0.70 and 0.79, it needs revision; <0.70 warrants elimination [152].

In the 1980's Lynn's research into the CVI suggested that acceptance values were determined by the number of validators [145]. Lynn calculated the proportion of experts who might agree out of the total number for planned use, and then set the standard error of proportion to identify acceptable CVI values for between 2-10 experts. This led to the publishing of Lynn's widely cited CVI values, which vary according to the number of experts. These findings suggested that for ≤ 5 experts, 100% agreement (CVI = 1.0) is necessary, but with six or more validators, one or more validators may be in disagreement, and a lower CVI (between 0.78-1.0 depending on the number of experts) may be acceptable [145].

Building on Lynn's work, Polit and Beck (and later Polit et al) proposed the use of different standards for I-CVI and S-CVI. Disagreeing with Lynn's standard-error approach, Polit et al linked the CVI to a modified-kappa index with the aim of setting I-CVI standards and recommendations for instrument developers to reference. In providing standards for different evaluations ('fair', 'good' and 'excellent') of content validity, Polit et al's conclusions at the I-CVI level were similar to Lynn's; a tool with I-CVIs of ≥ 0.78 will have 'excellent' content validity.

As discussed (see **17.6**), two definitions have been proposed for S-CVI; S-CVI/Ave, the more liberal, mean-based approach to S-CVI calculation, and S-CVI UA, the more conservative universal agreement approach. Given the more forgiving nature of S-CVI/Ave, Polit et al argue that the standard 0.8 acceptance value (and by extension, the 0.78 standard proposed for I-CVI) is too liberal a value to indicate excellent content validity at the scale level for S-CVI/Ave. In addition, Polit et al highlight that the mathematically identical ACP validity assessment adopts a higher benchmark of

0.9. Whilst the 0.8 value may present an acceptable, and even strict acceptance value for S-CVI/UA Polit et al conclude that an overall acceptance value of 0.9 for S-CVI provides a good intermediate between the liberal and conservative approaches.

17.11 Critique of the Content Validity Index

One of the main historical criticisms of CVI has been that the methodology does not address the possibility of chance agreement between experts [145]. To reduce the impact of chance inflation, Lynn developed widely-cited criteria for I-CVI acceptability which incorporated the standard error of proportion into item level calculations (see **17.10**) [145]. Polit et al, disagreeing with Lynn's standard-error approach, linked the CVI to a modified-kappa index which adjusts for chance agreements on relevance, as opposed to chance agreements of any type. In doing so, a set of I-CVI standards and recommendations were created for instrument developers to reference without the need to calculate the modified kappa [153].

A further argument against the CVI process states that the specifications and expectations of the process exceed practical application and the process is therefore too rigorous [145]. The process may be unsatisfactorily time-consuming in incidences where data is hoped to be gathered quickly.

In addition, researchers must hold into consideration that by design, the CVI measures all aspects of an item, and not solely domain relevance. A low CVI may indicate concerns regarding readability, language choice, and operational functionality in addition to the item's direct relevance to the domain. A low CVI could also indicate poor communication of the content domain or assessment methodology to the validator, and even indicated bias or inadequate domain knowledge on the part of the validator [153].

17.12 Determining Content Validity

Content validity of the survey questionnaire was assessed using a two-step process. First, following the CVI methodology outlined by Lynn and built on by Polit et al, content experts (referred to as 'validators' in communications) were asked to complete a validation questionnaire, indicating how relevant they thought each survey question was to the survey's aims [145, 153]. Second, each expert was invited to a virtual debriefing discussion. This was to address concepts that could not be covered in the validation questionnaire, to allow responses to the questionnaire to be elaborated upon, and to allow informal and organic discussion in relation to the survey and overall project.

17.13 Validation Tool Design

A validation questionnaire was designed (using Microsoft Word) to assess the content validity of the survey by quantifying I-CVIs/an S-CVI (see **Appendix 4**). For operational ease and differentiation of documents, the validation questionnaire document was referred to in all communications as the 'validation questionnaire', and the survey questionnaire document was referred to as the 'survey'. The validation questionnaire presented each question from the survey and asked each expert to identify how relevant they thought the question was to the survey aims on a 4-point scale (see **Fig. 11**). The validation questionnaire document also included an introduction to the survey and the wider project, a list of the survey aims, and a 1-page 'Validation Guide' to assist experts with the validation process.

Knowledge gap questions (see **17.1**) were presented only as the individual theme, and did not include a question frame. This was to ensure that any concerns on the wording of the question frame ('*I need to know more about…*' repeated for all 43 questions in this section) would not affect the content expert's responses to the relevance of the individual themes. Experts were informed

Least Relevant ◄——————————► Most Relevant			
1	**2**	**3**	**4**
☐	☐	☐	☐

Figure 11: Validation Questionnaire Validity Scale, as included in the Validation Questionnaire: 1= least relevant, 4 = most relevant, with a double-headed arrow between to signify increasing/decreasing relevance

of this in the validation guide. Discussion on the wording of the question frame was included in the debriefing discussion.

For clarity and ease of document navigation, the survey aim(s) (see **23**) that each question was designed to address was listed in the validation document next to that question. No 4-point relevance scale was included for the survey's introductory and closing texts, however the experts were invited to provide any comments that they had on these sections.

To guide the debriefing discussions, a 'debriefing checklist' was designed (see **Appendix 5**). The checklist was designed to gather information in relation to relevance that could not be assessed using the 4-point scale. This included discussions on the method of asking knowledge gap questions (primarily the question frame '*I need to know more about…*'), the use of jargon, and survey length. The checklist also provided a space for the investigator to confirm expert responses to any questions that the expert had missed or completed incorrectly, and confirm demographic information.

17.14 Selection of Content Experts

The selection criteria for content experts was defined as:

- Individuals with a professional involvement in pharmacovigilance/medicines safety in LMICs.

Efforts were made to target validators working in, or with experience working in LMICs, and also to target individuals representing a range of geographic locations.

Potential validators were identified via a number of strategies:

- Previous expressions of interest, or involvement, in GPV activities.
- Signposting to potentially relevant individuals by coordinators of alternative TGHN member hubs.
- Informal literature searches to identify published authors on pharmacovigilance activities in regions of interest.
- Referral to additional relevant individuals by contacted validators (snowballing).

17.15 Engaging Content Experts

All content experts were initially approached via e-mail and provided with an electronic copy of both the survey, and the validation questionnaire. Further information on the project was provided upon request, either in written form or via a virtual introductory meeting.

17.16 Expert Review

The content experts were asked to complete the validation questionnaire (see **Appendix 4**) by indicating how relevant they thought each survey question was to the survey aims using the 4-point scale of relevance (see **Fig. 11**). The experts were also asked to record any additional thoughts including those related to readability, word choice, definitions, or further comments on question relevance in the validation questionnaire document. The document could be completed virtually or printed and completed physically.

Following return of the completed validation questionnaire, all experts were then invited to a virtual individual debriefing discussion. If this was inconvenient or impractical for an expert, a virtual copy (Microsoft Word file) of the debriefing checklist (see **Appendix 5**) was provided by e-

mail for them to complete and return. Debriefing discussions were held using whichever communication platform was most convenient for the expert, which included Microsoft Teams, Google Meet, Skype and WhatsApp. Discussions were informal and sought to answer the questions listed in the debriefing checklist, as well as to allow organic discussion on the project themes in the expert's country or region. Information on response latency (the amount of time taken to complete the survey) was also gathered during this discussion.

Content experts were asked to provide their job roles, their country of residence, their number of years of experience in pharmacovigilance and any supporting information that clarified their interest in pharmacovigilance activities in LRSs.

17.17 Quantitative Data Analysis: CVI Calculation

Content validity of the survey was determined using the CVI. An I-CVI was calculated for each survey question, thus allowing S-CVI/Ave to be calculated for the overall survey. As previously discussed (see **17.6**), I-CVI for each individual question was calculated as the proportion of validators that had rated the question as a '3' or '4' on the 4-point relevance scale:

$$I - CVI = \frac{Number\ of\ Validators\ Scoring\ Question\ as\ Relevant}{Number\ of\ Validators}$$

S-CVI/Ave was then taken to be the mean of these values:

$$S - CVI/Ave = \frac{Sum\ of\ I - CVI\ Values}{Total\ Number\ of\ Questions}$$

Acceptable CVI values, as based on the literature (see **17.10**) were defined as follows:

- I-CVI: ≥0.78
- S-CVI/Ave: ≥0.90

Questions with an I-CVI <0.78 were removed from the survey. All quantitative data was processed using Microsoft Excel.

17.18 Qualitative Data Analysis

Qualitative feedback on the survey (written comments in the validation questionnaire document, comments from the debriefing discussion and further comments received via e-mail or other media) and validator demographic information was collated and reviewed on an individual basis. Suggestions for additional pharmacovigilance themes to be included in the knowledge gap questions and items to include/remove in demographic questions were noted. Comments relating to terminology were considered and changes made when deemed appropriate. Any formatting, typographical or spelling errors noted by the validators were amended.

17.19 Second Round of Expert Review

Second round testing followed a similar questionnaire process to the first round, although debriefing conversations were not conducted. A smaller pool of validators was selected for the second round, as suggested by Polit et al [153]. Five validators were re-contacted in accordance with Lynn's recommendation of 3-5 (see **17.9**), and to allow for non-responses and still be above the minimum recommendation (n=3). Experts were drawn from the same pool as round one to allow purposively sampling according to their first round responses (round one validators who selected only 'Strongly Agree' or 'Strongly Disagree' responses were excluded, as were those with a lower level of qualitative feedback), level of experience and speed of response. All second round

validators were contacted at least 20 days after debriefing conversations from the first round had taken place.

I-CVIs were calculated for new and amended questions, with those achieving an acceptable level of agreement then being included in the final survey. An S-CVI/Ave was then calculated for the final survey.

17.20 Face Validity

Face validity was assessed using a panel of global health researchers and health care workers, including a subsample of the population of interest (see **23**). The survey was uploaded and formatted using the Jisc Online Surveys tool (see **17.1**) and distributed to the panellists. Panellists were contacted selectively, and a minimum of 12 responses was sought before progressing, as advised in the literature [148]. Panellists were asked to work through the survey and review it in regards to functionality, organisation, readability, timing and typographical errors. Responses were then collated and amendments made where deemed necessary.

As an in-depth understanding of the survey's domain was not required to assess face validity, only a very broad selection criteria was set for the panellists:

- Previous experience in Global Health Research and/or familiarity with pharmacovigilance activities.

18 Consensus Building Methods: Survey

Following completion of the robust process of questionnaire design and validation outlined in section **17**, an online cross-sectional survey was launched to identify the highest priorities for pharmacovigilance in LMICs at that point in time during the COVID-19 pandemic (Sep-Oct 2021).

18.1 Recruitment

The inclusion criteria for survey participation was membership of TGHN. Participation was self-selective, and open to all individuals able to access to link to the online questionnaire (see below). This initially included participants that were not TGHN members prior to survey distribution, however all participants were required to register as TGHN members (if they had not done so previously) as part of the survey process.

18.2 Distribution

A link to the online survey was distributed to potential participants via:

- GPV's mailing list.
- Directly on GPV (via a dedicated webpage, highlighted across GPV).
- Across other relevant hubs on TGHN using promotional graphics (see **Fig. 12**)
- TGHN social media (Facebook, Twitter, LinkedIn).
- GPV social media (Twitter).
- Targeted communications to relevant individuals and organisations, with encouragement to share the survey within their organisations, and with other relevant individuals (snowballing).

A minimum four-week time period was agreed for the survey, and a minimum response rate (taken as a proportion of GPV membership at the start of Sep 2021, n=6000) of 5% (n=300) was sought. If



Figure 12: Graphic used to promote the survey across social media and TGHN.

the 5% response rate target was not achieved after four weeks then extension of the survey period would be considered (see **27** and **28.1**). The entire GPV membership* received the survey link via invitation email in week one. Reminder emails were distributed to GPV members in weeks three and five. In addition, social media was repeatedly utilised throughout the survey period to boost the survey's visibility. Promotional graphics were designed to support these activities (see **Fig. 12**).

19 Consensus Building Methods: Workshop

Given the inability to distinguish clear priorities following the results of the survey, and the high volume of additional challenges and concerns raised in the qualitative feedback, it was decided to undertake further consensus-building activities to further elucidate the greatest challenges facing pharmacovigilance in LRSs during the COVID-19 Pandemic.

* Excluding those that had previously unsubscribed from the GPV mail list.

19.1 Development

All survey participants were kept informed of the plan to host a virtual workshop via email following the survey's completion, and whilst analysis of the survey results was undertaken. This included provision of a proposed workshop date, title, and format:

> '*The session [proposed workshop] will begin with a presentation of the recent survey findings, followed by an open discussion during which attendees will be invited to share their thoughts on the survey outcomes, pharmacovigilance priorities in their settings, and the way forward. Attendees will also be invited to join novel working groups that will work collaboratively to address the priorities identified*.'
>
> **Excerpt from 'update email' sent to survey participants, Dec 2021**

A later update email (Jan 2022) was disseminated as workshop plans progressed.

Software

The cloud-based proprietary videoconferencing software Zoom was selected as the host technology for the workshop for the following reasons:

- Desirable functionalities including customisable registration forms (see below), presentation sharing, written messaging ('chat'), 'Q&A', interactive polling (see below) and recording.
- Operability on both desktop and mobile devices.
- The ability for attendees to join the workshop without an account registered to the software and at no cost.
- Researcher familiarity with the software.
- Ease of use of the software.

- Existing Zoom licence held by TGHN offering the ability to support a large audience. (max. 1000 workshop attendees).

Zoom's 'Webinar' feature was used to host the workshop.

Registration Form

Attendees were required to register for the workshop in order to attend. Zoom's customisable registration form (part of its webinar feature) was utilised to present introductory information on the workshop's background and aims, and to collect registrant/attendee demographic data including country, job role and work institution.

Poll

Zoom's polling feature was utilised to gather further consensus on the highest priorities for pharmacovigilance during the COVID-19 pandemic in LMICs at that stage of the pandemic.

Zoom's various polling options were tested in advance of the workshop (with the support of a team of global health researchers) before a decision was made on the most appropriate option.

A two question poll was designed (see **Appendix 11**). Question 1 (multiple-choice) presented the 10 highest pharmacovigilance priorities identified in the survey, and asked participants to select three elements of pharmacovigilance that they believed to be the current highest priority at that point in the COVID-19 Pandemic (where support, training and guidance are needed). Question 2 (single choice) asked participants whether they felt that the 10 pharmacovigilance themes listed where currently relevant to their setting.

The software did not provide the option to apply a response limit to question 1. Thus, whilst it was intended that participants select three options from the answer list only, in practice participants

could submit fewer or more responses than requested (range =1-10). To address this, polling instructions indicating that three (and only three) options should be selected were included as written instructions in both the polling answer window and the holding slides (see **Appendix 11**), and were repeated verbally by the researchers before and during the polling period.

19.2 Identifying a Workshop Chair

GPV members were invited to chair the workshop. Survey participants were invited to propose themselves or others as potential workshop Chairs in the update email sent in Dec 2021.

After the receipt of proposals for a workshop Chair(s), a decision on an appropriate Chair was made following consideration of the proposed Chair's availability, level of experience, publication history, location (LMIC vs HIC) and involvement in international pharmacovigilance activities.

The potential Chair was then approached via email and provided with further information as to what the chairing role would involve, and further details regarding the workshop. This included a draft 'Workshop Guide' (see **Appendix 10** and below) for the proposed Chair's comments and input. An introductory virtual meeting was also arranged (Jan 2021) to allow a formal introduction between the proposed chair and the researchers, elaborate further on the workshop plan, present the findings of the survey and provide a more detailed background to the project, and to address any concerns or questions that the Chair might have. Following this meeting, an agreement was reached that the proposed Chair would Chair the workshop.

Note: A panel of Chairs was recruited for the workshop chairing role. This is discussed in greater detail below, (see **31**).

Chair Preparation

A date and time for the workshop was agreed with the Chairing Panel. As discussed, a 'Workshop Guide' document (see **Appendix 10** and above), was developed and received input from the Chairs. The document included an agenda, key text including introductions and housekeeping notes, notes on software management, and notes to the Chairing Panel to support the discussion period.

A virtual workshop 'practice session' was arranged three days prior to the workshop to ensure software familiarity (eg allow the practice sharing of presentations and test-run 'chat 'and poll functionality), discuss the proposed running order, introduce TGHN's digital support team and address any of the Chairing Panel's concerns or queries. Additional ad-hoc virtual meetings were arranged in the lead-up to the workshop when requested.

19.3 Dissemination and Promotion

Promotion of the workshop began a week in advance of the event. Workshop invitations and information were disseminated via the following channels:

- 2 TGHN research hub (GPV, COVID Hub) mailing lists.
- Directly on GPV (via a dedicated webpage, highlighted across GPV).
- Across other relevant hubs on TGHN using promotional graphics (see below).
- TGHN social media (Facebook, Twitter, LinkedIn).
- GPV social media (Twitter).
- Chairing Panel's organisation's social media, website, and in-house communications (newsletter).

In addition, more comprehensive updates were emailed to survey participants that had expressed an interest in remaining updated on the project activities.

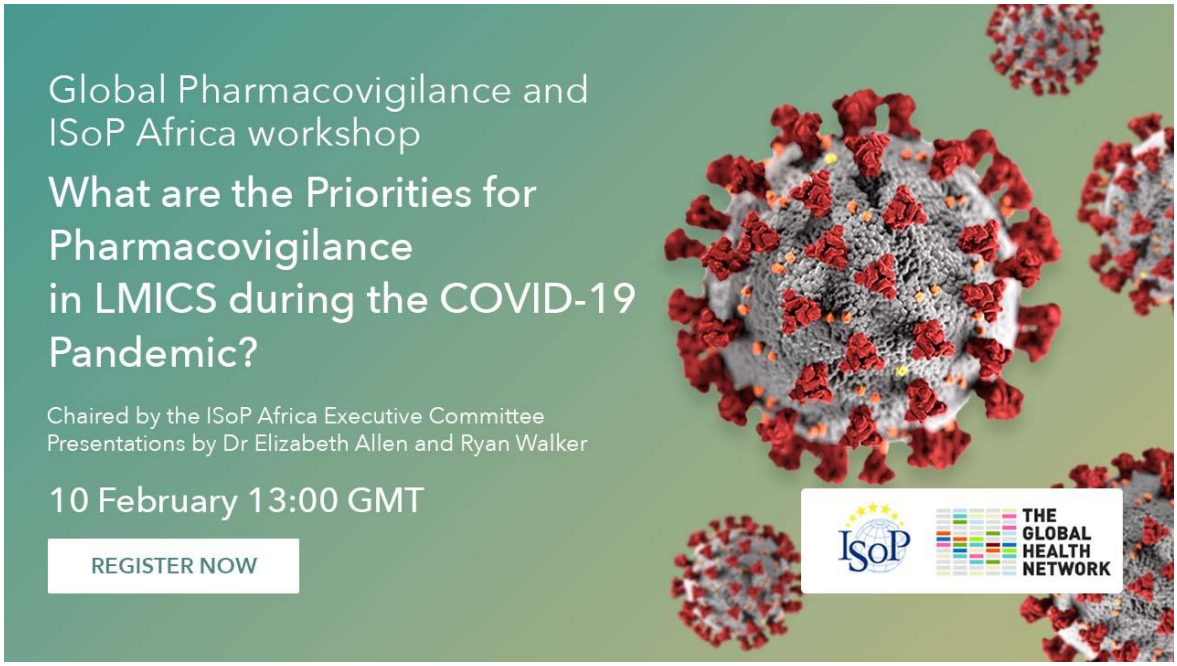


Figure 13: Graphic used to promote the workshop across social media and TGHN. A similar amended version, featuring the full names of the chairs (n=4), was used as a holding slide during the workshop.

Promotional graphics for the workshop were designed with support from TGHN's digital team and approval from the Chairs (see **Fig. 13**). These graphics were used to support the event dissemination described above, and during the workshop itself.

19.4 Workshop Format

For a summary of the Workshop Agenda, see **Appendix 10**.

Pre-workshop Checks

Presenters, Chairs and TGHN Digital Support team were invited to join the Workshop up to 30 minutes in advance to make final checks and preparations, including connectivity checks, sound tests, software tests (presentation sharing etc), and to discuss any final questions or concerns. At this point the workshop was not 'live' and was therefore inaccessible to registrants.

Introductions

The workshop was 'opened' so that registrants could join the session. A member of the Chairing Panel introduced the workshop and provided 'housekeeping information' (instructions for software usage, disclaimers on data collection, attendee microphone etiquette, etc). The Chair then gave a short presentation on their organisation and the rationale for the collaboration between their organisation and GPV on the workshop.

Presentations

2 presentations were given by GPV researchers (DPhil candidate and co-supervisor/GPV coordinator). The first presentation provided an overview of GPV (background, development, the platform's place within TGHN, and current activities) and TGHN. The second provided a background to the current project, a description of the survey design, and presented the results of the survey.

Questions and Answers

A question and answer ('Q&A') period, moderated by a member of the Chairing Panel, was held to allow participants to ask questions in regards to the two presentations.

Open Discussion

An hour-long discussion period, moderated by the Chairing Panel, was initiated to allow participants to share their thoughts on the pharmacovigilance priorities identified in the survey. Participants were invited to share their comments verbally, and if that wasn't possible then via written response in the chat and Q&A boxes. Questions that were used to guide the discussion are included in **Appendix 10**.

Explanation of Working Group Plans and Poll

A GPV researcher explained the intention to create working group to address the elements of pharmacovigilance that participants believed to be the highest priorities at that point in the COVID-19 Pandemic where support, training and guidance were needed. It was explained that quantitative and qualitative data (in the form of poll results, and thematic analysis of the discussion respectively) would inform the domain of focus for each working group.

An in-workshop poll was then run (see **19.1**). The poll remained answerable for a period of five minutes, before it was 'closed' (no longer visible to attendees). Instructions on how to answer the poll were given verbally (both before and during the polling) and visually (in writing as part of the workshop slide deck, and as part of the poll question itself).

Closing Remarks

Closing remarks and thanks were given by a member of the Chairing Panel before the workshop was ended.

19.5 Post-Workshop Poll

A post-workshop poll was created immediately after the workshop to address technical issues encountered during the in-workshop polling (see **32.5**). The post-workshop poll was developed using the online survey software Jisc (see **17.1**).

This poll featured the same two questions from the in-workshop poll, in which the question wording, formatting, and response order remained identical. In addition, respondent contact information was also requested to prevent the duplication of data from the in-workshop poll.

Unlike Zoom (see **19.1**), Jisc features an option to limit response numbers in multiple-choice questions. In the post-workshop poll, a forced response number of three was applied to question 1 (see **Appendix 11**).

The post-workshop poll was emailed to workshop attendees who explicitly indicated (via the in-workshop chat) that they were unable to complete the in-workshop poll on the day following the workshop. The poll remained live for seven days, and a reminder email was sent to those who had not yet completed the survey by day five.

19.6 Quantitative Analysis

Quantitative data (attendee numbers, demographics and polling data) were extracted from Zoom/Jisc and underwent descriptive analysis using MS Excel. Contact information from the post-workshop poll submissions was cross-referenced with the in-workshop submissions to ensure that no participant made multiple submissions.

The in-workshop and post-workshop poll results were combined for final analysis. A plurality block vote approach was used to determine the highest-ranking priorities:

- Attendees were asked/required to select three priorities from a list of 10.
- The 10 priorities were the ranked by their total number of votes.
- The three priorities with the highest number of votes were used to inform future activities.

19.7 Qualitative Analysis

The Q&A and discussion periods of the workshop were transcribed to facilitate qualitative analysis. Qualitative data (Q&A transcript, discussion transcript, written Q&A responses and written comments in the 'chat box') underwent thematic analyses using NVivo 12 Pro.

Non-English qualitative responses (see **31.1**) were translated into English by global health researchers who were native speakers of the respective languages before analysis.

20 Implementation Methods: Working Groups

Following the identification of the highest priorities for pharmacovigilance in LRSs during the COVID-19 pandemic, where greater support, education and guidance were needed, it was decided to establish working groups to facilitate the collaboration of GPV members in addressing these priorities.

GPV members were invited to join working groups to address the highest priorities for pharmacovigilance in LMICs following the survey and workshop. Working groups were established for each of the three highest-ranked priorities following the workshop poll (see **31.1**).

20.1 Forming Virtual Working Groups

An online working group registration form was designed using the survey software Jisc (see **17.1** and **Appendix 15**). The form consisted of eight questions and invited participants; to identify which of the three working groups they had an interest in joining, to identify if they were interested in taking on a coordinating role within any of the working groups and to gather demographic and contact information. As with the initial survey, demographic questions were deliberately featured at the end of the form (see **17.1**). Participants were able to express an interest in both joining and taking a coordinating role in multiple working groups. Information on the activities that had informed working group formation (survey and workshop), potential group activities and outcomes, and further explanation on which participants might be interested in a coordinating role (see **20.2**) were provided in the invitation email and registration form's 'Welcome' page.

Working group invitation emails, featuring a link to the registration form, were distributed in March 2022. Invitation emails were sent to workshop registrants first before being distributed to the entire GPV membership five days later. A dedicated webpage inviting membership to the working groups and featuring a link to the registration form was also featured directly on GPV. The registration form remained live until Aug 2022, to allow continual growth of the working group membership throughout the initial working group activities.

Unlike during the survey and workshop dissemination, the working groups were not advertised on GPV/TGHN social media. This was for three reasons;

- To specifically target workshop registrants and existing GPV members to foster a sense of community and inclusivity.
- To allow time to gauge community interest in each group. If group registration numbers were deemed to be too low, then promotion on social media would be considered to increase engagement.
- Workshop registration data suggested that GPV/TGHN mail lists were by far the most effective method of gathering registrations/achieving responses.

20.2 Forming Coordinating Groups

All working group participants were invited to take on a coordinating role within their respective working groups. Participants were able to indicate their interest in a coordinating role in the working group registration form, and then via personal communication with the existing group coordinators thereafter.

The working group invitation email and registration form welcome page specified the following:

'In addition, if you have experience working in any of the areas listed above [working group themes listed], we invite you to take on a coordinating role in that working group'

Similarly, question 2 of the working group registration form appealed to those with experience in the working group areas to volunteer for a coordinating role (see **Fig. 14** and **Fig. 15**).

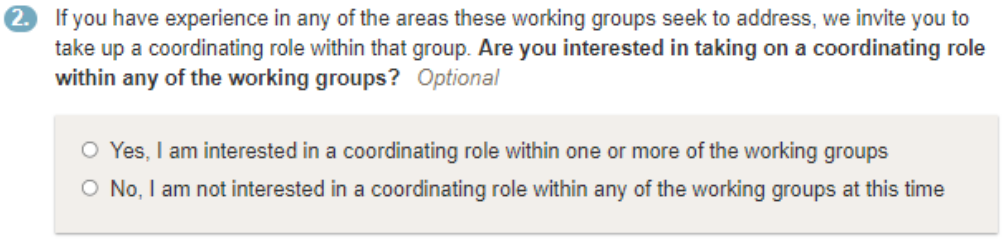


Figure 14: Question 2 of the working group registration form inviting those with experience in the working group thematic areas to take up a coordinating role within that respective group(s). Question response was optional, to avoid forced answering and potential 'over-selection' of interest in a coordinating role by community members that may not have had relevant experience. The negative option was deliberately phrased to be time independent; 'No, I am not interested… at this time', to convey to participants that they would be welcome to join the coordinating group at a later point, and to express the informal nature of time commitment and participation in the working groups.

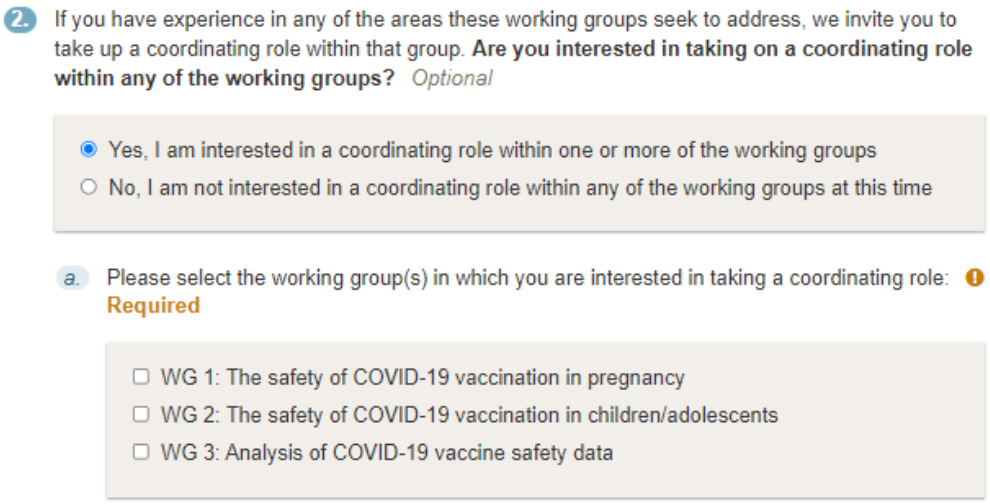


Figure 15: Question 2 of the working group registration form with positive option selected, causing display of dependent Question 2a. No dependent question was displayed when selecting the negative option for Question 2. If participants indicated an interest in a coordinating role (optional), they were required to identify as to in which working group.

20.3 Coordinator Introductory Meetings

All participants that had indicated an interest in a coordinating role in any of the working groups were invited to a virtual 'Coordinator Introductory Meeting' for each of the working groups that they had selected. An email invitation to these meetings was sent to all relevant participants in April 2022 (following a three week period to allow for completion of the working group registration form) to all those who indicated that they were interested in a coordinating roll at that point in time. The invitation emails included a registration link for each meeting, meeting agendas and outlined the meeting aims.

All three introductory meetings were held on separate days in the w/c 11/04/2022. The meetings were held in ascending order of group membership (at that point in time) to allow any issues encountered in the meeting format, presentations or agenda to be addressed prior to the larger meetings. Each meeting was scheduled for 1hr and occurred at the same time each day (11am BST). 11am BST was selected as the meeting time following consideration of the geographic distribution of working group participants.

The aims of each coordinator introductory meeting were as follows:

- To allow the introduction of group members interested in a coordinating role.
- To provide more information to attendees on each working group's overall membership.
- To expand on what a coordinating role might involve.
- To suggest potential working group plans and activities.
- To invite discussion on potential working group activities and outcomes.
- To answer any questions or concerns regarding the working group(s).

Each introductory meeting was hosted using Zoom and followed a similar format:

- Short (15-20min) presentation given by GPV representative to attendees, providing:
    - A background to the working group and the wider project.
    - Demographic data of all working group registrants, including location (country), profession, institution and experience in pharmacovigilance to provide an overview of the working group 'make up'.
    - An example of TGHN's previous experience in supporting research-based working groups (COVID Hub), which included the presentation of existing working group specific webpages, resources and outputs.
    - Proposed 'next steps', which included an agreement for meeting participants to form the coordinating group, the working group theme to be expanded upon and a topic for focus within that theme determined, and discussion of potential group outputs.
    - An expansion on what the coordinator role might involve (see below)
- Attendee introductions
- Discussion period (approx. 30 mins) to address the 'next steps' outlined above, and to answer any questions attendees may have had on the working groups.
- Agreement of action points.

It was explained to the attendees that the exact nature of the coordinator role was to be determined by the group, in order to ensure that activities are group-led. It was noted that:

- The role will be voluntary (no remuneration)
- It is envisaged that the role will be informal
- No time or workload commitments will be specified by GPV/TGHN, however the group is welcome to set defined commitments if it is deemed necessary.

- No leadership positions (eg ‘Group Lead’, ‘Chair’, ‘President’ etc) will be allocated by GPV/TGHN however the group is welcome to create leadership positions if it is deemed necessary.

It was further outlined that GPV/TGHN will play a supportive role in all working group activities and in facilitating group research (eg In the provision of an online space for group activities, supporting group communication, supporting the development and sharing of resources, facilitating professional connections, etc) but it was hoped that all activities and outcomes would be ‘group member-led’.

Each meeting was recorded to allow the accurate taking of minutes. All attendees were informed that the meetings were being recorded, and consent was gained for the sharing of attendee data, contributions to the discussion (both verbal and written in Zoom’s ‘chat box’), and discussion summation to be shared with the wider group membership.

A meeting report was produced for each of the coordinator introductory meetings and disseminated to all working group members in an ‘update email’ within two weeks of each meeting. The meeting reports included an attendee list, a summary of each meeting’s presentations and discussions, and the demographic data for each group (at that point in time). Each meeting report was shared with the attendees of each relevant coordinator introductory meeting for comment and review before being shared with the wider group.

20.4 Taking Working Group Activities Forwards

Coordinator emailing lists were established for each working group following the Coordinator Introductory Meetings. These mailing lists consisted of all coordinator meeting registrants (both attendees and non-attendees), and participants that had not registered for the meeting but had expressed an explicit wish to be involved in coordinating activities via personal communication.

These participants were thereafter considered to be the Group Coordinators, unless they later requested otherwise.

In addition to the 'update email' disseminated to all working group members (see above), follow-up communications were continued with the coordinators via the mail lists. The first communications (May 2022) sought to introduce group coordinators who had been unable to attend the coordinator introductory meeting(s), to encourage discussion regarding the action points raised in the meeting, to share resources relevant to the group theme, and to encourage coordinators to share any relevant resources or materials that they might have.

Following the initial coordinator meeting, meetings were continued on a monthly basis. All meetings were held virtually using Zoom Agendas were created and distributed pre-meeting, as were minutes and relevant actions points post-meeting. Meeting topics and discussions were guided by the participants, and the focus of each meeting was guided by the discussion of the previous. Action points and group outcomes were also determined and undertaken following group discussions.

21 Coordinating the Global Pharmacovigilance Platform

No formal methods were adopted to guide platform activities as developments and outcomes were led largely from reaction to ongoing global pharmacovigilance work. The activities also did not form a formal component of the action research approach outlined in **Fig. 10.** The majority of developments were either undertaken to improve the usability of the platform, in response to member request or contributions, or to support this thesis' research activities (see **37.3)**.

Data on platform usage was gathered using Google Data Studio, and is presented in terms of 'sessions'. A 'session' is defined as a continuous period of time that a user is active on GPV. By default, if a user was inactive for ≥30 minutes, any future activity is attributed to a new session.

Users that navigate away from GPV and return within 30 minutes are counted as part of the original session.

22 Timeline Overview

A detailed timeline of major methodological milestones is presented in **Fig. 16.**

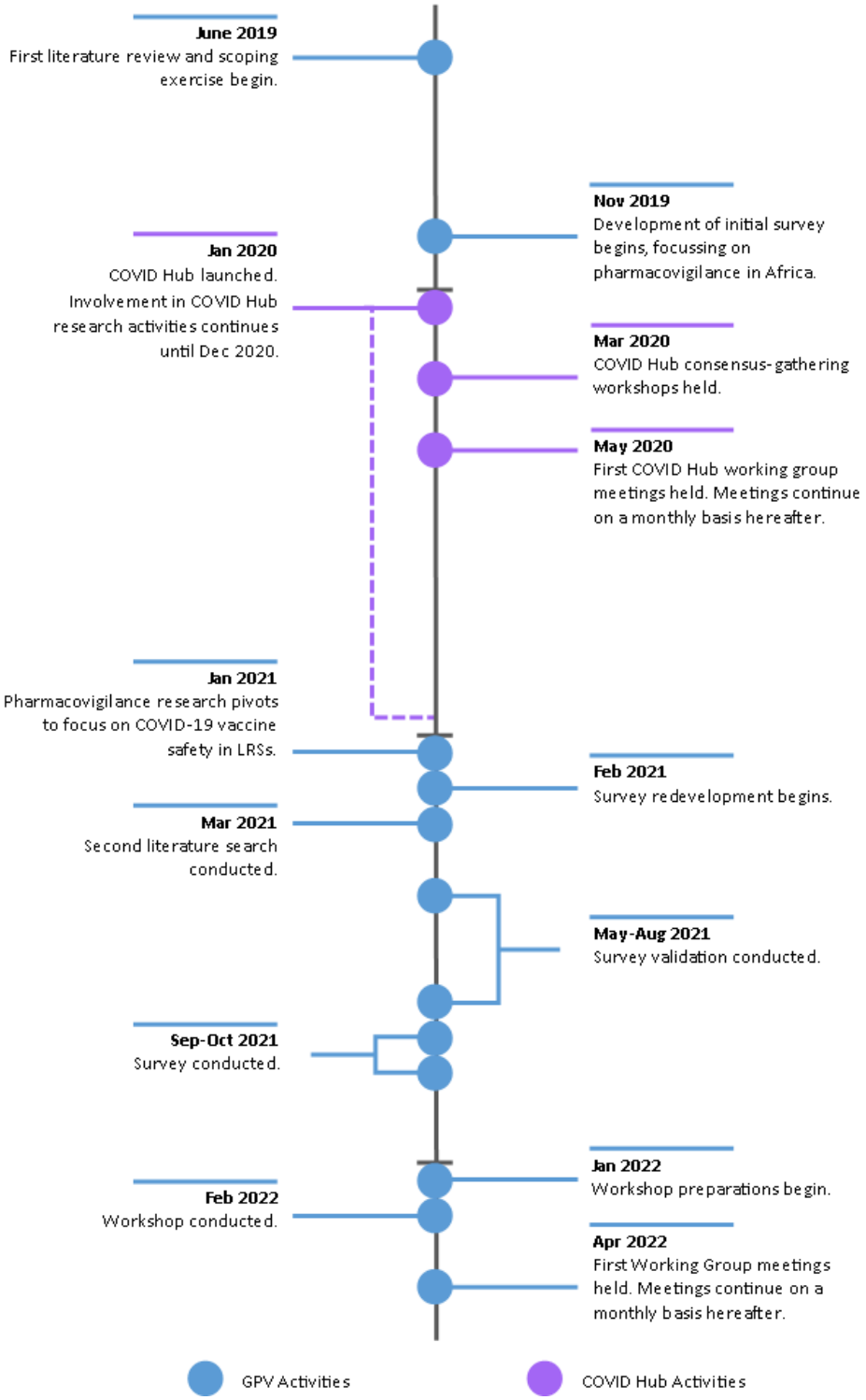


Figure 16: Timeline of major methodological milestones

Part III: Consensus Building Results

IV Survey Validation

The process of survey validation initiated the first action research cycle of this research. A comprehensive overview of the validation methodology has been provided in the previous chapter (see **17**). The component stages of the research cycle were met as follows:

- **Plan:** Investigated validity assessment methods (see **17.2 - 17.11**).
- **Act:** Development of validation tools and engagement of content experts (see **17.13**, **17.15**, **Appendix 4** and **Appendix 5**).
- **Observe:** Collected data, calculated CVIs and reviewed expert feedback (see **17.16**, **17.17**, and **17.18**).
- **Reflect:** Reviewed need for further validation, considered value of process, considered experts comments on pharmacovigilance in LRSs (see **17.19**, **25** and **Appendix 7**).

For a visual representation of the validation methods applied to the action research cycle, see **Fig. 17**.

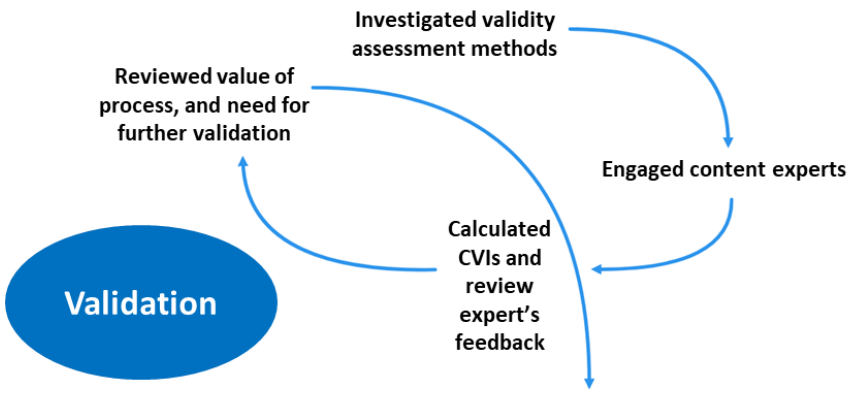


Figure 17: Survey validation methodology within the action research cycle. Adapted from **Fig. 10**.

23 Survey Objectives

- To identify and prioritise pharmacovigilance knowledge gaps in LMICs, with specific relation to the COVID-19 pandemic.
- To gather demographic data in order to better understand the population that makes up the pharmacovigilance CoP.
- To assess attitudes towards pharmacovigilance within the pharmacovigilance CoP.
- To gather data on the usage and user experience of GPV.

24 Results

Content Validity testing took place over a period of three months between May and Aug 2021. A total of 16 individuals, each working in, or with experience in, pharmacovigilance were invited to validate the survey. Of this 16, two individuals did not respond to the introductory email, two responded to the introductory email but then did not provide completed copies of the validation questionnaire, one offered 'informal advice' on the survey but did not complete the questionnaire[*], and one declined to complete the questionnaire due to language barriers. In total, 10 individuals provided responses and acted as content experts.

Face Validity testing took place over a two week period in Sep 2021. A total of 14 individuals, working in global health research/and or with familiarity with pharmacovigilance activities reviewed the questionnaire.

[*]This advice was considered alongside qualitative feedback from the rest of the validators during review.

24.1 Content Validity Testing: First Round Quantitative Results

Content Validity Expert Demographics

Eight different geographical regions were represented by the 10 content experts (based across nine different countries), with two experts having experience in pharmacovigilance activities in regions additionally to where they were based (see **Fig. 18**). The 10 experts had a collective 182.75 years of involvement in pharmacovigilance, and an average involvement of 18.3 years. The longest period of pharmacovigilance involvement was 40 years, and the shortest was nine months.

A range of professions and background were also represented. 'Academic' was the profession most frequently represented (n=4), but the panel also included a pharmacovigilance scientist, a pharmacoepidemiologist, a programme manager of a public health agency, a pharmacovigilance manager of a public research institution, a technical expert in pharmacovigilance and a national principal pharmacist. Many additional roles and backgrounds were represented amongst the



Figure 18: Regions represented by questionnaire validation content experts. Content experts are shown according to UN geoscheme sub-region (see **25.2**). Subregions represented (n=9); South America, Caribbean, Northern Europe, Western Africa, Eastern Africa, Southern Africa, Southeastern Asia, Australia and New Zealand, *Melanesia.

content experts, including experience as pharmacists, medical doctors, medicines regulators and experience in the pharmaceutical industry (eg qualified persons for pharmacovigilance). Two panellists had recently retired from full time work but remained involved in the field.

CVI: First Round

An I-CVI was calculated for all questionnaire items (n=58). All survey items scored I-CVIs ≥0.78 (range 0.80-1.00). S-CVI/Ave for the questionnaire following first-round content validity testing was 0.93.

During analysis, it was identified that eight content experts (80%) had either not completed all required responses, or had completed some responses incorrectly (eg selected multiple responses for one item). This was raised with the validators during the individual debriefing discussions, and responses were either completed/corrected during the discussion, or provided by the validators via email following the discussion.

24.2 Content Validity Testing: First Round Qualitative Results

Validation Questionnaire Feedback from Validation Questionnaire

Qualitative feedback received from the validation questionnaires included recommendations of additional items for inclusion (see **Fig. 19**), advice on language choices, comments on item design and questionnaire structure (see **Fig. 20**), identification of typographical and formatting errors and suggestions for factors to consider when analysing results.

Comments on language choice included the reduction of jargon, clarification of existing terms. Recommendations on item design included expansion of existing items (question text), and expansion/reduction of existing response options. Feedback relating to questionnaire structure

Validation Questionnaire

- I need to know more about case definitions of AESIs
- I need to know more about AEFI/AESI detection in clinical trials
- I need to know more about the causality assessment of AEFIs/AESIs
- I need to know more about the safety of non-COVID-19 vaccines
- I need to know more about the safety of COVID-19 vaccination in immunosuppressed patients
- I need to know more about how to effectively communicate COVID-19 vaccine/medicine safety information
- I need to know more about COVID-19 vaccine/medicine related safety reporting systems in other countries/regions
- I need to know more about how to access COVID-19 vaccine/medicine safety data.

Debriefing Discussion

- I need to know more about the safety of COVID-19 medicines in special patient groups (pregnancy, elderly etc).

Figure 19: Recommendations for additional knowledge gap questions in the questionnaire. Eight of these recommendations were received from validation questionnaire qualitative responses, one was developed following debriefing discussions.

focused on the positioning and order of demographic questions, inclusion of explanatory information, and addition of novel/removal of existing items (**Fig. 20**).

Validation Questionnaire Feedback from Debriefing Discussions

An overview of the topics discussed in the debriefing discussions, the general consensus amongst the content experts regarding each topic, and the action taken following the debriefing discussions is outlined in **Table 8**.

Pharmacovigilance Challenges in LRSs

Several validators provided comment on the challenges facing pharmacovigilance in LRSs in both the validation questionnaire and debriefing discussion. An overview of the key challenges raised,

Theme	Action	Example	Relevant question(s) in final questionnaire	Example Quote(s)
Language Choice	Reduction of Jargon	Change 'breastfeeding' to 'lactation'.	Q4.1	*"The term off-label/unlicensed would not be well understood as most [countries in validator's region] do not have a regulatory control system of licensure in their countries"*
		Change 'therapeutics' to 'medicines used to manage COVID-19'.	Q5	
		Change 'off-label/unlicensed'.	Q5.4	
		Change 'physician' to 'doctor'.	Q11	*"Define 'physician' more. Doctor, clinician, clinical officer?"*
	Clarification of terms	Provide a definition of pharmacovigilance.	n/a	*"At this point, best to indicate what is the person's role. In LMICs, those in government doing PV may not be a singular task. It might be one pharmacist doing multiple roles and PV is not really a focused job and not prioritized."*
		Redefine 'day-to-day role'.	Q13	
Item Design	Expand existing items	Include mention of 'vaccines' in scope of pharmacovigilance.	Q1	*"Reduce to three or four choices."*
	Expand existing response options	Include additional/amend existing roles and institutions.	Q11, Q12	*"Too many choices."*
	Reduce existing response options	Reduce Frequency options in frequency-based questions.	Q9, Q13	
Questionnaire Structure	Refine demographic question order	Include all demographic questions at the same point in the questionnaire.	Q11-Q16	*"Suggest you explain here that the questions will focus on vaccine vigilance and COVID-19 therapeutics"*
	Improve explanatory information	Include a list of questionnaire topics.	Page 3 Text	
	Add additional, non-knowledge gap items	Involvement in COVID-19 intervention trials/ safety studies.	Q15	*"It may be worth asking your respondents if they have been involved in clinical trials/COVID vaccine development, or if they are performing a post marketing study"*
	Remove existing Items	Removal of items with little perceived value.	n/a	

Figure 20: Qualitative feedback on questionnaire design received from validation questionnaire responses

Questions Raised in Debriefing	General Consensus	Action Taken
Question frame for knowledge gap questions	Responses were largely positive, however some validators suggested rewording, or providing further details, such as defining 'need'.	No action taken, as clear consensus on a need to amend the question frame was not achieved. Note made to discuss the impact of question frame on survey outcomes.
Repetition of patient group section for therapeutics	No clear consensus was reached on the need to repeat this section. Many validators provided no decisive opinion on this issue.	Section not repeated for therapeutics, however, as per a validator's suggestion, a single knowledge gap question was added to the therapeutics section: '*I need to know more about therapeutic challenges in special patient groups (pregnancy, elderly etc)*'.
The use of jargon	The majority of validators expressed no concerns regarding the technical terms used in the survey. Nevertheless, some validators had highlighted specific concerns and suggested alternative terminology in the validation questionnaire.	Amendments made to specific terms highlighted in the validation questionnaire (**Fig. 20**). It was also ensured that all acronym definitions were clearly visible when relevant.
Survey length	The vast majority of validators deemed the survey length to be acceptable.	No action taken. Note made to establish accurate completion time during face validity assessment, for inclusion on questionnaire introductory page
Any other thoughts	Several validators reiterated suggestions and comments made in the validation questionnaire. Some validators also acknowledged that the 'readability' of the questionnaire was acceptable. In addition to providing comments on the questionnaire, several validators provided their thoughts on the challenges facing pharmacovigilance in LRSs.	Additional questions suggested included in second round validation (see **Fig. 19**). Comments on the challenges facing pharmacovigilance in LRSs collated and included in analysis (see **Appendix 7**).

Table 8: Survey validation debriefing discussion outcomes

Theme	Challenges Raised in Qualitative Feedback
Systems	Need for organisational strategy Need for operational management Lack of medicines regulation Need for strong political will of national pharmacovigilance agencies
Data Generation	Many HCPs don't know what to report Low incentive to report HCPs only report serious AEs Minimal patient reporting Poor quality reports
Knowledge and Attitudes	Pharmacovigilance is a poorly understood term Low health literacy Pharmacovigilance viewed by many HCPs as a work target, not part of everyday practice
Medicines	Poor quality medicines are common Limited access to medicines
Data Access	No baseline data of background rates Data silos
Human Resources	Not all relevant stakeholders are engaged Limited healthcare workforce Lack of cross-discipline pharmacovigilance training Lack of dedicated pharmacovigilance staff
Financial Resources	Lack of financing for pharmacovigilance activities
Cultural Factors	Black magic/superstitions believed to be the cause of ADRs
Medicating Practices	Poor compliance

Table 9: Challenges facing pharmacovigilance in LRSs raised by survey validators

grouped thematically, are outlined in **Table 9**. These challenges are discussed in detail in **Appendix 7**.

Amendments to Questionnaire

Following consideration of both qualitative and quantitative data, the following amendments were made to the survey:

- 2 Items (relating to whether or not respondents worked primarily in pharmacovigilance, and level of pharmacovigilance training) were removed, following concerns raised of the value and necessity of these questions during the validation questionnaire and debriefing discussions.

- 2 items (relating to pharmacovigilance experience, and frequency of engagement in pharmacovigilance activities,) were reworded, following concerns raised about the of the language choice during the validation questionnaire and debriefing discussions.
- 10 new items were developed (see **Fig. 19**, and additional question related to involvement in COVID-19 intervention trials/safety studies, see **Fig. 20**) following suggestions raised during the validation questionnaire and debriefing discussions.
- Where acronyms were used, it was ensured that acronym definitions were immediately visible.
- Response options in frequency based questions were reviewed and reduced (from n=7 to n=6).
- An explanatory page, featuring no questions, was included prior to the knowledge gap questions to clearly outline the aims of that section, and provide an overview of the upcoming question topics.
- All demographic questions were moved to the end of the survey.
- Typographical errors, formatting errors, and changes to jargon were made when necessary.
- All new and amended survey items were included in the 2nd round CVI assessment.

24.3 Content Validity Testing: Second Round Quantitative Results

The decision to perform a second round of content validity testing was made following analysis of the qualitative responses received during CVI testing and individual debriefings (see **24.2**).

Of the five content validators re-contacted for second round review, three responses were received. The average years of involvement in pharmacovigilance of the second round validators was 27.33. UN

Questionnaire Version	I-CVI Range	S-CVI/Ave	S-CVI/UA
Questionnaire following 1st round CVI test	0.80 – 1.00	0.93	0.45
Questionnaire following 2nd round CVI test	0.67 – 1.00	0.93	0.5
Final Questionnaire	0.80 – 1.00	0.94	0.52

Table 10: Questionnaire CVI scores at all stages of testing. Minimum acceptable I-CV =0.78; Minimum acceptable S-CVI/Ave=0.90. S-CVI/UA was not utilised as a measurement of instrument validity but was calculated for reference.

geoscheme sub-regions represented were Eastern Africa, Southeastern Asia and Australia and New Zealand, with one validator having previous experience in Melanesia.

Of the items included in the second round of content validation (n=12), three scored I-CVI's <0.78 and were removed from the questionnaire. The remaining nine items (seven novel items and two reworded items from round one) were included with items from round one to form the final survey. See **Table 10** for an overview of CVI values. 63 items were included in the final questionnaire.

24.4 Face Validity Testing

14 individuals who fulfilled the selection criteria participated in face validity testing. This included global health researchers, HCPs, and members of the survey's population of interest (see **14**). The panel included participants from both LMICs and HICs, and panellists whose first language was not English.

The panellists reviewed the questionnaire in the intended format for survey participants (via the Jisc online platform, see **17.1**) and provided feedback either via email, comments in the free text sections of the questionnaire, or in person.

Comments were received regarding functionality, readability, typographical errors and response latency (time taken to complete the survey). Amendments were made to the questionnaire based

on these comments when deemed necessary. Panellist responses to the questionnaire items were also used to perform mock data analyses.

Comments regarding response latency were reviewed, and an average completion timeframe of 10-15 minutes was determined. This was then included in the questionnaire 'welcome' page.

25 Discussion

25.1 Questionnaire Validity

The final questionnaire demonstrated a high level of content validity (final I-CVI range = 0.80-1.00 [≥0.78]; final S-CVI/Ave = 0.94 [≥0.90], see **17.17**). This suggests that the questionnaire was an effective tool for meeting the survey aims and that the items included in the questionnaire provided an exhaustive and accurate representation of the domain of interest, namely pharmacovigilance priorities in LMICs during the COVID-19 pandemic.

The extensive validity testing process, including the CVI assessment, debriefing discussions, and face validity testing, ensured that the questionnaire was reviewed by a wide range of individuals which in turn assured that the questionnaire demonstrated effective functionality and operability, and also exhibited an acceptable level of readability.

25.2 Content Expert Diversity

A diversity of settings, experience levels, and professional roles were represented amongst the content experts. Similar diversity was also noted amongst the face validity panellists. This variation in background and circumstance was considered a valuable asset to the validity testing process, as it ensured that perspectives were gathered from across the entirety of the pharmacovigilance spectrum. Moreover, building on Grant and Davis' advice that a geographically diverse pool of

experts increases the chance of identifying colloquial terms and phrasing, and on Lynn's recommendations to consult ≥5 content experts to control for chance (see **17.7**) it is postulated that ensuring the diversity of both the background and circumstances of content experts (as in this research) reduces the potential impact of questionnaire bias towards particular regions, professions or experience levels [145, 161].

'Academic' was the profession most frequently represented by content experts (n=4). This is an unsurprising outcome, given that one of the strategies for content expert selection involved the identification of published authors on pharmacovigilance activities in regions of interest. Despite this majority, this was not considered to introduce any significant bias towards pharmacovigilance stakeholders working in academia into the questionnaire. Academia is a diverse field and academics working in pharmacovigilance may be involved at a variety of points on the pharmacovigilance spectrum, including clinical, regulatory and drug development activities. Indeed, 75% (n=3) of the experts that identified as academics indicated previous or concurrent experience in another pharmacovigilance-related role (regulatory affairs, medical practitioner/regulator, QPPV). The specific fields of interest of the academics involved in content validation were not captured in this research.

For the presentation of geographic data, content experts were deliberately grouped via UN geoscheme sub-region as opposed to being listed by their specific country. This was to ensure expert anonymity, as in some of the experts' countries there were very few individuals working in pharmacovigilance, and combinations of detailed demographic data had the potential to make content experts identifiable. Seven of the UN geoscheme sub-regions represented either predominantly or wholly included LMICs (South America, Caribbean, Western Africa, Eastern Africa, Southern Africa, Southeastern Asia and Melanesia).

25.3 Uncertainties Encountered With the CVI

Despite an in-depth review of the CVI literature and a rigorously outlined CVI assessment methodology, several unforeseen obstacles were encountered whilst assessing content validity. Primarily, these related to disparities between quantitative and qualitative results. Note that the collection of qualitative feedback, in addition to the use of the 4-point Likert scale, is a recommended part of the CVI process [145].

Firstly, the question arose as to how to proceed when the I-CVI for an item was deemed acceptable (ie ≥0.78) but incidences of negative qualitative feedback suggested that the item needed further consideration. This occurred with four items following the first round of content validity testing. An overview of the questions concerned, their respective I-CVIs and qualitative feedback suggesting removal/amendment are shown in **Table 11**.

Secondly, the question arose as to how to proceed when the S-CVI/Ave for a tool was deemed acceptable (ie ≥0.90) but qualitative feedback identified additional items for inclusion in the survey. This occurred in the first round of content validity testing, when the S-CVI was deemed to be acceptable, but content experts had suggested additional items for inclusion in the questionnaire (see **Fig. 19** and **Table 10**).

In both of these incidences, the quantitative results (CVI values) suggested that no further action was necessary, as all I-CVIs in question and the S-CVI/Ave were above the acceptable minimum value (see **Table 10**). All items, and the overall instrument, could therefore be deemed content valid, and it could be concluded that the items and the instrument (without further amendment) fully assessed the target domain.

By contrast, reasonable concerns were raised regarding some items via qualitative feedback, which upon consideration, it was decided warranted further action (see **Table 11**). Similarly, a number of additional items were suggested for inclusion in the questionnaire **(Fig. 19),** despite the first-round

Question	I-CVI	Qualitative Feedback Example(s)	Action
'Do you work primarily in pharmacovigilance?'	0.80	*'I don't find this useful; Q3 provides more detail.'* *'Questions 3 and [this question] are not the same - yet they are overlapping. Is there a need to have both?'*	Removed
'Which of the following describe(s) your level of training in pharmacovigilance? Please select all that apply.'	0.90	'*Even those with no formal PV training can have a good grasp of PV so I am unsure if that is what you are drawing conclusions about or not?*'	Removed
'How frequently do you engage in pharmacovigilance activities in your day-to-day role?'	1.00	'*How will this help you decide on value based on frequency of engaging in PV? Don't you think this is dependent on who is answering the question? Doing it say, 'once a year', does it make PV less important? They could be working on big data analysis that can generate signals, or [be] a committee head who makes the decision to delist a drug or to allow its continued use*.'	Amended
'How long have you worked in pharmacovigilance?	1.00	*'Many will have spent many years in PV but with many other roles as well so you are missing those who have responsibility for PV in country but it is not their primary role.'*	Amended

Table 11: Items included in the first round of content validity testing that scored an acceptable I-CVI but were amended or removed from the questionnaire. PV = pharmacovigilance.

S-CVI/Ave score indicating that the instrument already fully assessed the target domain. If qualitative data had not been collected and analysed and only the CVI scores had been used to determine content validity, these legitimate and valuable concerns would have gone unconsidered.

This conflict demonstrates a limitation of quantitative CVI data as a solitary measure of content validity, and the value of collecting and analysing qualitative data to compliment the CVI process. No guidance was identified in the literature regarding how to proceed in this situation. In this incidence, qualitative feedback was reviewed on an item-by-item basis and appropriate action

taken when deemed necessary. Despite the acceptable CVI scores, it was considered necessary to conduct a second-round of CVI testing (see **17.9** and **17.19**) in order to ensure/establish the validity of the amended items/additional items proposed, and by extension the collective validity (S-CVI/Ave) of the amended questionnaire.

The inclusion of new survey items in the second round CVI assessment raised additional concerns regarding questionnaire length. Nevertheless, it was considered important to assess the validity of the expert-suggested items, to ensure the highest possible level of overall questionnaire content validity. The questionnaire expanded by a total of seven items between first round validity testing and the final questionnaire, and no concerns regarding questionnaire length were raised during second round content validity and face validity testing.

It is acknowledged that the greater number of content experts consulted, the more likely it is that such conflicts will arise. These findings support Lynn's hypothesis that 10 content experts (as consulted in this research) is an appropriate maximum number of experts for a CVI assessment) (see **17.7**) [145]. Greater numbers of content experts are more likely to provide conflicting qualitative feedback and create further uncertainty for researchers.

It is unlikely that definitive criteria can be set to guide future researchers who encounter similar uncertainties when using the CVI, as this will depend upon the nature of the qualitative feedback received, in addition to operational considerations such as human resource capacity and researcher timescales. In addition, researchers should consider the potential impact on response rates that may result from excessive questionnaire length following the addition of expert-suggest items. Nevertheless it is highly recommended that researchers collect qualitative feedback as part of a content validity assessment, and conduct a thorough review of this data before concluding that an instrument is content valid.

25.4 Value of a Second Round of Content Validity Testing

A second round of content validity testing was undertaken following consideration of qualitative feedback to the first round, as described above. Following removal of items with an I-CVI <0.78 after the second round, S-CVI/Ave increased by only 1.1% (n =0.01, 1st round of testing S-CVI/Ave = 0.93; final questionnaire S-CVI/Ave = 0.94, see **Table 10**). No change was noted in the I-CVI range.

This minimal increase in S-CVI/Ave, and the lack of effect on the I-CVI range, calls into question the value of a second round of content validity testing in this incidence, especially given a previously determined excellent level of validity (First Round S-CVI/Ave =0.93) and the time consuming nature of a repeated CVI assessment This further serves to highlight the confusion presented by conflicting quantitative and qualitative CVI data described above. In spite of this, due to the foundational aspect of the survey to this body of research it was deemed imperative to ensure the greatest possible rigour in determining survey validity as possible.

25.5 Debriefing Discussions Outcomes

Debriefing discussions were used to gather content expert's opinions on particular questionnaire features that could not be assessed effectively using Likert-type items. An overview of these topics is provided in **Table 8.**

Question Frame

Of particular interest was the need to determine whether or not the method of asking questions in the questionnaire provided an understandable and logical way to identify the priorities for pharmacovigilance in LRSs during the COVID-19 pandemic. In particular, this focussed on how the knowledge-gap questions were presented, and whether the question frame 'I need to know more about [pharmacovigilance theme]' (**Fig. 21**) provided an accurate measure of the target domain.

I need to know more about…	/	…terminology used in vaccine PV
Question Frame		Pharmacovigilance Theme

Figure 21: Example knowledge gap question structure. This specific example was Q2.1 in the final questionnaire (see **XIII8**). PV = pharmacovigilance.

It was acknowledged that the use of the phrase '*I need to know more about…*' in this questionnaire assumes that a participant's subjective opinion of their personal knowledge gaps can equate to a 'pharmacovigilance priority'. Nevertheless, content experts were largely supportive of the use of this question frame for determining pharmacovigilance priorities:

> '*It is a good way of asking the question as it makes the respondent think about their* answer'
>
> **Clinical Researcher, Western Africa**

> '*No problems with this, the individual approach is a good approach to the question'*
>
> **Pharmacovigilance Scientist, Northern Europe**

> *'Many issues in LMICs are not knowledge gaps but institutional and systems based concerns eg management, funding, strategies. Nevertheless, I am happy with the question frame for the needs of the survey.'*
>
> **Academic, Southeastern Asia**

As alluded to in the final quote, some experts suggested amendments to/further considerations for the question frame:

> *'It may be helpful to define what you mean by 'need'. I had to think to make sure I defined my needs, and not my 'want'.*
>
> **Pharmacovigilance Manager, South America**

Other content experts suggested potential options for rephrasing, and repetition of the knowledge gap questions with the question frame rephrased to explicitly focus on prioritisation.

Given the critical aspect of question framing to the overall outcomes of this research, feedback on question framing was reviewed in detail. Ultimately, as no clear consensus was reached on a need to restructure the question, no action was taken. Nevertheless, it was decided that a discussion of the potential impact of the question frame upon identifying 'priorities' should be included in the discussion of the survey's results (see **28.5**).

COVID-19 Medicines in Vulnerable Groups

Another matter for consideration was as to whether the section '*COVID-19 Vaccine Pharmacovigilance According to Patient Group*' should be repeated with a specific focus on the pharmacovigilance of medicines used to manage COVID-19 according to patient group, as it was realised that the majority of knowledge gap questions focused on vaccine pharmacovigilance, and no specific question relating to the safety of medicines used to manage COVID-19 in vulnerable groups had been included in the '*Pharmacovigilance of Medicines Used to Manage COVID-19*'.

No clear consensus was determined regarding this issue. Some content experts felt that the there was no need to repeat the section, whilst others thought that it would be useful:

> *'Vaccines are the priority' [and hence there was no need to repeat the section for medicines]*
>
> **Hospital Pharmacist/Pharmacoepidemiologist, Eastern Africa**

> *'This depends on who is being asked, if the survey is aimed towards prescribers and patient groups, maybe include a repeat for therapeutics. If it is aimed towards 'higher level' people and regulators, maybe ignore*.'
>
> **Pharmacovigilance Scientist, Northern Europe**

'It would be good to repeat the section for therapeutics to gather a more comprehensive picture of priorities.'

Clinical Researcher, Western Africa

Several other experts indicated that they were unsure as to whether the section should be repeated or not. As no clear consensus on the need to repeat the patient group section for COVID-19 medicines was reached (accompanied by concerns about drastically increasing survey length, see below) the decision was made not to repeat the section. Nevertheless, a compromise was implemented; upon the suggestion of a content expert (Academic, Southern Africa), a single item was added to the 'Pharmacovigilance of Medicines Used to Manage COVID-19' section: *'I need to know more about the safety of COVID-19 medicines in special patient groups (pregnancy, elderly etc)'.*

Jargon and Survey Length

Concerns regarding specific terminology were primarily raised by content experts in the validation questionnaire (see **Fig. 20**) although experts were asked to provide their opinions on the 'overall technicality' of the language choice used in the questionnaire during the debriefing discussions. General consensus was that the language choice was appropriate for the intended participants and the aims of the survey, and no problems were noted with the language used even by those whose first language was not English:

'The use of technical terms are fine, anyone expecting to have some knowledge of pharmacovigilance should know these terms.'

Academic, South Eastern Asia

'If you work in or have an interest in pharmacovigilance, you should be familiar with these terms'

Pharmacovigilance Scientist, Northern Europe

The majority of content experts indicated that they felt that the survey length was acceptable, although some indicated that they felt the questionnaire was '*a little long*' or that it was '*a bit lengthy*'. One expert explicitly cautioned against the inclusion of additional items; *'I need to emphasize that I think the length of this survey is just right and the longer it gets the fewer responses you will have*'. These comments were taken into consideration when considering the addition of further items to the survey

Pharmacovigilance in LRSs

Whilst the validation process was not designed to robustly collect qualitative data relating to the general challenges facing pharmacovigilance in LRSs, debriefing discussions were harnessed as an opportunity to learn more about the research themes in each content expert's country or region. These comments underwent a basic thematic analysis, which is presented in **Appendix 7**.

25.6 Value of Debriefing Discussions

The debriefing discussions provided a valuable opportunity to gather consensus and provide clarity on critical aspects of the questionnaire, regarding which the researchers had identified reservations, and of which it was deemed impractical to gather feedback via quantitative methods. Furthermore, it was found that the uncertainties regarding these aspects could be better communicated verbally than in writing, and that an opportunity for content experts to provide comments in 'real time' generated more organic and in-depth discussion.

It is acknowledged that some aspects assessed in the debriefing discussion could have been measured in the validation questionnaire (eg opinions on the use of jargon and survey length, indeed, all actioned reduction of jargon was a result of comments received from the validation questionnaire, see **Fig. 20).** In reality, researchers considering the adoption of a similar hybrid

content validity testing process should carefully consider whether or not the inclusion of debriefing discussions are likely to add value to their results. If relatively short, simple tools seeking to test well-established concepts are being assessed, debriefing discussions may be unnecessary. If however researchers are looking to generate feedback on more complex structural elements of a tool (as in this research), the use of debriefing discussions may prove very valuable.

The questionnaire elements that were assessed in the debriefing discussions demonstrate the overlaps between content and face validity (see **Table 7).** Whilst some aspects (question frame, the need to include further questions) are clearly within the remit of content validity, others (survey length, the use of jargon) are items commonly assessed in more rudimental face validity testing. Despite the confusion surrounding the demarcation of these two types of validity the assessment of items that overlap between the two types only serves to strengthen the validity and robustness of a tool.

25.7 Content Validity Testing Time

Whilst content validity testing took place over a period of approximately three months the development of validation tools (validation questionnaire, debriefing checklist, etc) began approximately two months in advance of the testing phase (Apr 2021), resulting in a total content validity assessment process spanning five months.

All validity testing was conducted virtually, via email and virtual communication platforms. Developing validation tools, identifying potential content experts, awaiting email responses, introducing the research to the content experts, awaiting completion of the validation questionnaire, arranging debriefing discussions and responding to expert's questions and requests were all time consuming processes.

It is acknowledged that the content validity testing period could have been shortened by consulting a smaller pool of content experts, providing further support to Lynn's hypothesis that 10 experts is an appropriate maximum number of content experts for a CVI assessment (see **17.7** and **25.2**) [145]. A greater number of validators would most likely have prolonged validity assessment unnecessarily. In addition it is acknowledged that the content validity testing period could be shortened if researchers were able to interact with content experts in-person, and/or if they had previously familiarity with the experts, however, this should not come at the cost of content expert diversity without justification (see **25.2**).

It is recommended that researchers consider the potentially time-intensive nature of this methodology before adopting it in their own research. The potentially 'over rigorous' nature of the CVI process has been previously raised in the literature (see **17.11**), and this is further exaggerated by the inclusion of an additional debriefing element [145]. This may be of particular importance to researchers who seek to undertake a rapid and/or immediate assessment of a particular phenomenon.

25.8 Value of the Hybrid Content Validity Testing Process

This research adopted a novel, hybrid approach to content validity testing which, to the best of the authors' knowledge, has not previously been described. When investigating instrument validity testing methods, it was decided that a quantitatively-driven approach such as the CVI would not sufficiently evaluate all aspects of the questionnaire. This was in part due to the multifactorial nature of the questionnaire (see **23**), and also the desire to seek expert-level feedback on both structural, and at times nuanced, aspects of the instrument.

The discovered limitations of the CVI (see **25.3**) demonstrate that it is not an infallible process. As demonstrated, the collection of qualitative data can raise important considerations regarding

instrument validity. Whilst it has previously been acknowledged that the collection of qualitative feedback is a necessary part of the CVI process, there does not appear to be any guidance on the interpretation of this feedback in the literature, and historically the determination of both item and scale-level content validity appears to be solely determined by quantitative results. This research has demonstrated that the collection of qualitative data is an important but previously overlooked element of a CVI assessment.

Nevertheless, as highlighted, qualitative data should be collected as an integral part of the CVI process. In this work, this was facilitated by the collection of qualitative feedback in the validation questionnaire. In actuality, the majority of the changes that were made to the questionnaire following first-round validity testing were done so in response to qualitative feedback received in the validation questionnaire, and not from comments received in the debriefing discussion (see **24.2**). This could call in to question the value of the debriefing discussion and the hybridised approach, particularly as some aspects assessed in the debriefing discussions (jargon, readability, functionality etc) were also assessed in both CVI and face validity testing, and also given the time-intensive nature of the hybrid content validity testing process described above (see **25.7**).

Despite these considerations, the hybrid approach was deemed a beneficial component of this research. Primarily, the holistic consideration of data gathered in both the CVI assessments and debriefing discussions provided a more accurate and 'real-world' picture of the questionnaire's validity. Although ultimately no consensus was reached on some of the uncertainties raised in the debriefing discussions (see **25.5**), the hybrid approach allowed for consideration of varied perspectives regarding these matters, and informed the reporting of the survey outcomes (see **28.5**). Moreover, given the foundational nature of the survey to this body of research, it was deemed essential to ensure the greatest level of validity as possible to ensure that future research activities were based on robust and accurate results.

The gathering of perspectives, insights and advice relating to the overall field of research was an additional advantage to the hybrid validity testing approach (see **Appendix 7**), however this should not be the primary motivation for adopting this methodology, and should only serve to compliment robust knowledge synthesis strategies, not replace them.

25.9 Terminology

It was noted that the term 'S-CVI' (Scale-Level Content Validity Indices), originally proposed due to its application to scale development (see **17.6**), is a potentially outdated descriptor of this instrument validity measure. S-CVI has been widely adopted to assess the content validity of a variety of instruments, by no means limited to scales (as in this research, and demonstrated in the literature). It is therefore proposed that the term 'Tool-Level Content Validity Indices' ('T-CVI') provides a more appropriate and universally-applicable label of the validity measure[*].

25.10 Face Validity

Face Validity testing provided an important opportunity to test the validity of the questionnaire in its final, 'participant-intended' format, as this was the first point in which the questionnaire was assessed within the Jisc survey tool. This allowed for the identification of any errors introduced to the questionnaire as part of the uploading process, as well as any concerns regarding formatting within the online tool, and the identification of formatting or typographical errors not identified during content validity testing. This ensured the functionality of the online questionnaire prior to the engagement of participants.

[*]'Instrument-Level Content Validity Indices' is a potential alternative, however this risks confusion with 'Item-Level Content Validity Indices' (I-CVI).

Mock data analyses were conducted on the panellist's responses (see **24.4**) to ensure that the questionnaire items were capturing relevant data, to clarify the analysis process, and provide researcher familiarity with the analysis functions of the survey software. In this sense, Face Validity testing provided the opportunity to conduct informal pilot testing.

26 Conclusion

The novel, hybrid approach to content validity testing described above can provide a rigorous and exhaustive method for determining the content validity of an instrument. Researchers considering the adoption of this hybrid approach should do so with careful consideration of its value to their own research and their available timescales.

The questionnaire that was assessed using this methodology is a highly valid tool for the assessment of priorities for pharmacovigilance in LRSs during the COVID-19 pandemic, and can be implemented to provide an accurate assessment of these priorities. An assessment of the results of this survey should include consideration of the questionnaire design and validity testing process.

The challenges encountered during the CVI process support Lynn's hypothesis that 10 content experts is a sensible maximum number of experts for CVI testing. In addition, the targeting of content experts with diverse backgrounds and settings reduces the likelihood of the introduction of bias and further increases the content validity of a tool. Furthermore, it is recommend that the more universal term 'Tool-Level Content Validity Indices/Index' (T-CVI) be adopted in place of S-CVI, particularly in incidences when the validity of a scale is not being assessed.

Future research should look to further investigate the incorporation of qualitative data analysis into content validity assessments, and it is recommended that the feasible of developing a criteria for the consideration of qualitative data alongside quantitative data in a CVI assessment be investigated. It is highly recommended that researchers adopting a similar hybridised approach to

that described here provided a thorough discussion of their methods and findings, in order to support future research in this area.

V Survey Implementation

Following completion of the survey validation, and reflection upon the validation outcomes and process, the survey was finalised based on the validity testing results, marking the initiation of the second action research cycle. A comprehensive overview of the survey methodology (see **17**) and the survey objectives (see **5** and **23**) are provided elsewhere. The component stages of the research cycle were met as follows:

- **Plan:** Finalised questionnaire based on validity testing outcomes (see **24.2** and **24.3**).
- **Act:** Launched survey (see **18.2**).
- **Observe:** Analysed quantitative and qualitative survey results (see below).
- **Reflect:** Considered survey findings, their implications for pharmacovigilance in LRSs, and whether clear priorities had been identified (see below).

For a visual representation of the validation methods applied to the action research cycle, see **Fig. 22**.

27 Results

The survey was conducted over a five week period between Sep-Oct 2021. After the initial four week survey period, the survey had received 111 responses (response rate = 1.85%). The survey period was extended for an additional week, after which a total of 156 responses were received (response rate = 2.6%).

Of the 156 responses, one response was excluded from the final analysis due to the identification of heavily politicised comments and references to vaccine misinformation (repeated references to '*greedy politicians'* and '*an experimental pseudo vaccine*') during preliminary analysis. The remaining 155 responses were included in the final analysis.

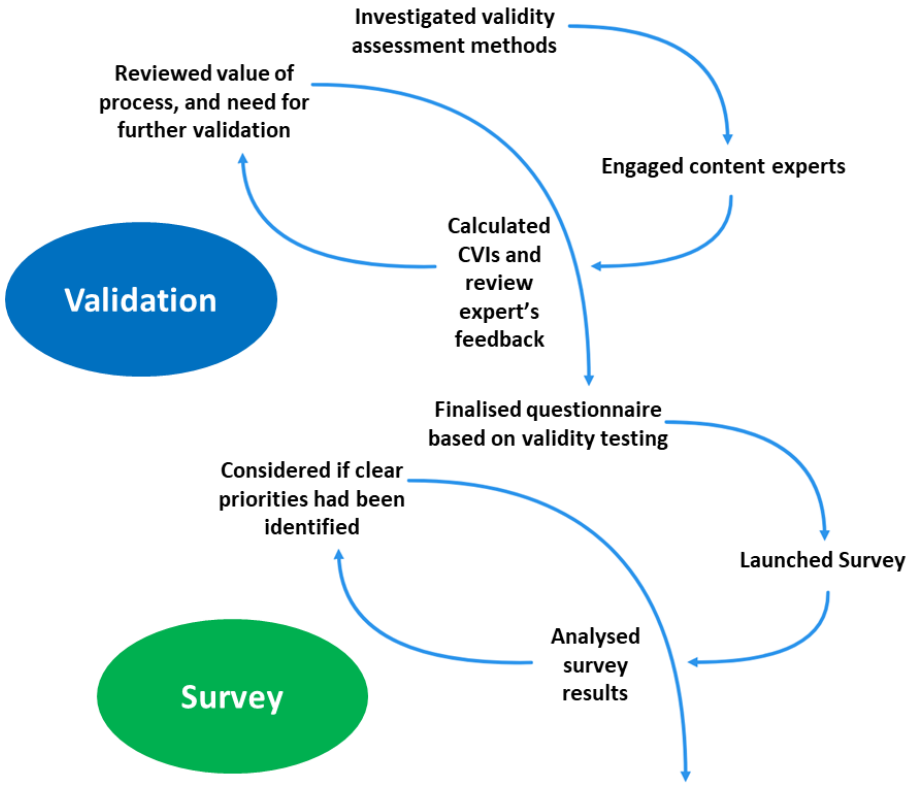


Figure 22: Survey methodology within the action research cycle. The approach to the survey has been informed by the outcomes of the validation, demonstrating the iterative process. Adapted from **Fig. 10**.

27.1 Quantitative Results

Demographics

Survey responses were received from 54 countries (**Fig. 23**). This included 38 LMICs (70.4%) and 16 HICs (29.6%). 85.2% of individual responses (n=133) were received from those based in LMICs. Nearly half of all respondents (49.7%) were based in Africa, with Asia being the second most represented region (24.5%). The countries most represented were Kenya (15.5%), India (14.8%), Nigeria (6.5%), Uganda (6.5%) and Ghana (3.9%).

Of the respondents from HICs (n=23), 10 provided further clarification regarding their interest or involvement in pharmacovigilance in LMICs, although precise reasoning could only be determined

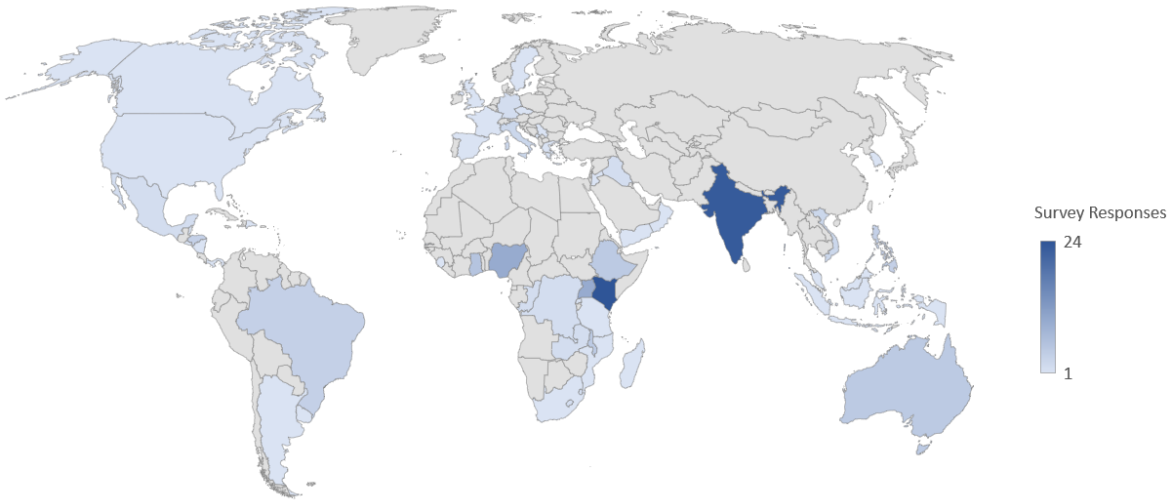


Figure 23: Countries represented by survey respondents. Not visible at this scale are The Gambia (n=1), Kiribati (n=1), Sint Maarten (Dutch Part) (n=1), Tonga (n=1).

from eight of these responses. Of this eight, five respondents indicated a professional connection to, or strong understanding of, pharmacovigilance in LMICs, two indicated general personal interest, and one respondent implied that the term 'HIC' may not accurately describe their setting. 1.9% of respondents (n=3) provided qualitative responses in a language other than English (Spanish n=2; French n=1).

A minimum of 12 professional roles were represented, and 44.5% (n=69) indicated that they held more than one role. 'Pharmacist' was the most common role held by respondents (49.0%), followed by 'Academic/Researcher' (34.8%) and 'Student' (15.5%) (see **Fig. 24.A**). 67.1% of respondents indicated a role as an HCP (Pharmacist, Doctor, Nurse, Dentist, Midwife and Clinical Officer). A quarter (25.2%) of respondents indicated a previous involvement in COVID-19 clinical trials, vaccine development or post-marketing safety studies.

A least 16 types of institution was represented by the respondents, and 41.9% (n=65) indicated that they worked for more than one type of institution (see **Fig. 24.B**). 'University/College' was the institution most commonly represented (35.5%) followed by 'Hospital (Public)' (31.0%) and 'Hospital (Private)' (12.9%).

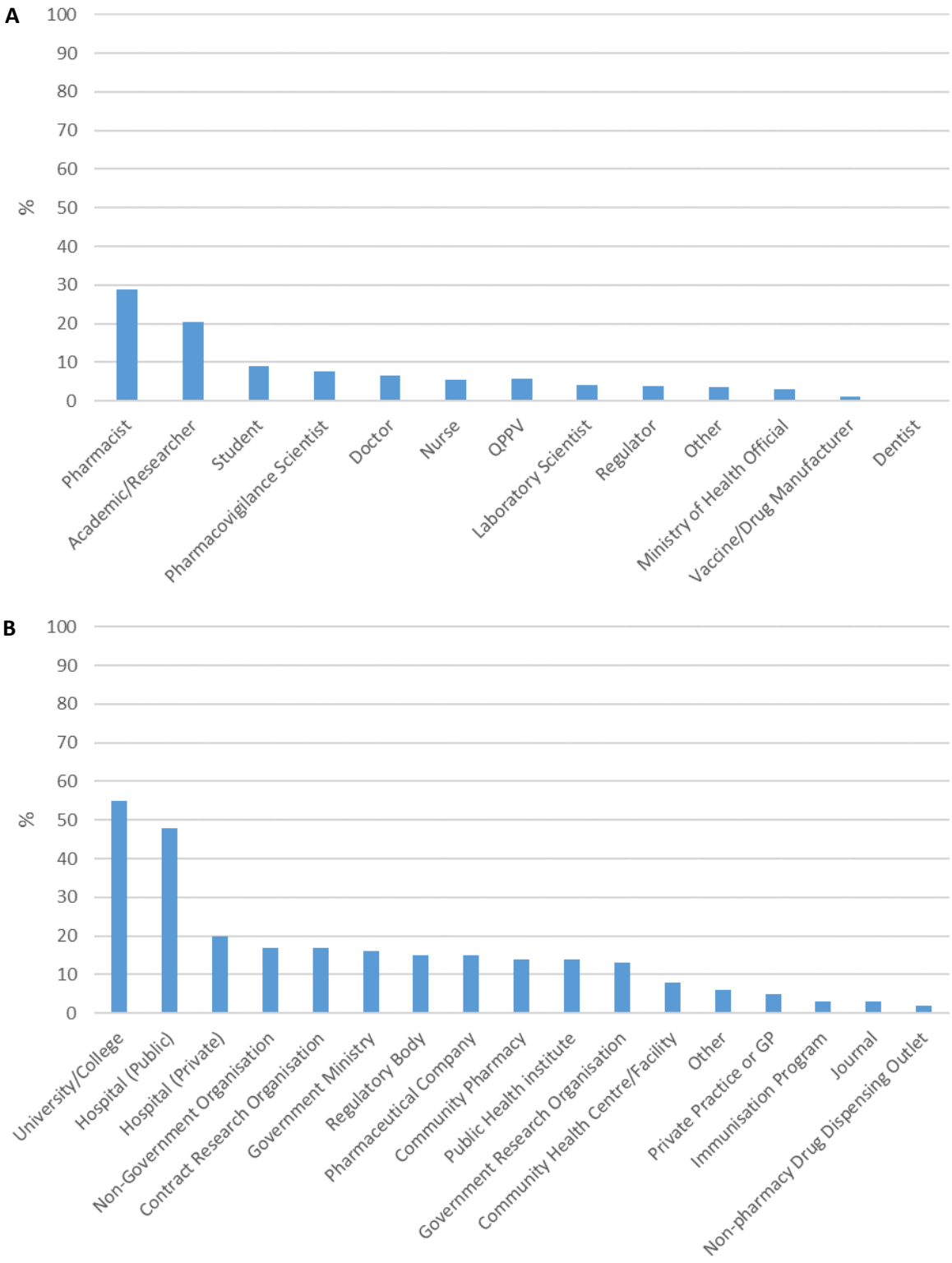


Figure 24: Job roles (A) and institutions (B) of survey respondents. GP = General practitioner. 'Other' responses for Job Role (**A**) included 'Public Health Logistician', 'Clinical Officer', 'Midwife', 'Pharmacologist', 'Pharmacovigilance Consultant', 'Health Officer', 'Animal Disease Surveillance Agent (Veterinarian)', 'Clinical Research Advisor' and an individual currently out of work, with pharmacovigilance experience in a pharmaceutical company. 'Other' responses for Institution (**B**) included consultancies (n=3), 'Clinical Genetic Laboratory', 'UN Agency' and voluntary support of pharmacovigilance activities.

Knowledge, Attitudes and Practices

The survey began with a knowledge-test question to ensure that all respondents had a basic understanding of the tenets of pharmacovigilance (see **17.1**). All participants selected at least one of the proposed definitions of pharmacovigilance, whilst 34.8% selected all of the applicable definitions (see **Fig. 25**). 1.9% (n=3) of respondents sought to offer an additional definition to those provided: in all cases this was in addition to selecting all definitions provided within the question. A majority of participants indicated that to them, pharmacovigilance meant at least one of the following; '*The detection and assessment of drug-related adverse effects*' (85.2%), *'Improving the safety, quality and efficacy of all medical interventions including herbal medicines, blood products and vaccines*' (76.1%) and *'The understanding and prevention of drug-related adverse effects*' (67.7%). A minority of respondents indicated that pharmacovigilance meant at least '*Encouraging the rational and effective (including cost-effective) use of all medical interventions*' (37.4%).

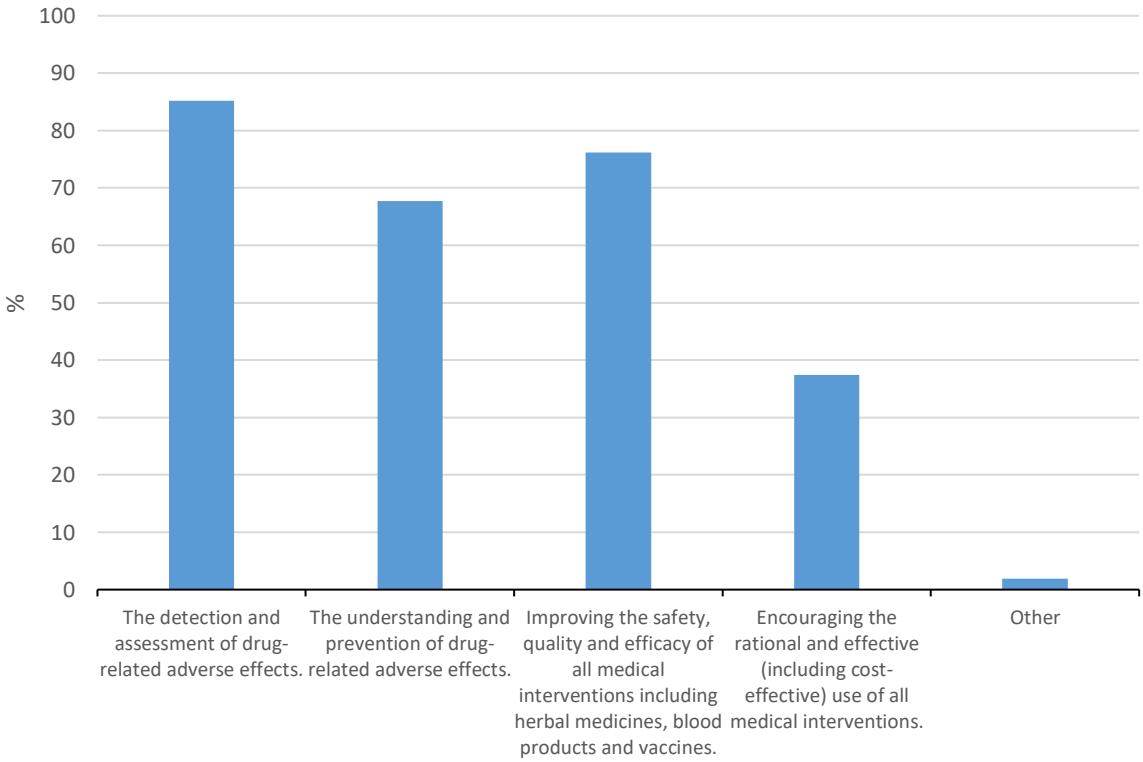


Figure 25: What does the term 'pharmacovigilance' mean to survey respondents? Mutliple answers could be selected. Values represent the percentage of respondents (n=155) who selected each answer option.

47.7% of respondents identified that they had been involved in pharmacovigilance for ≤5 years ('less than 1 year', 14.2%; '1-5 years', 33.6%), whilst a quarter of respondents (24.5%) indicated no involvement in pharmacovigilance at all. 11.6% of respondents had greater than 10 years involvement in pharmacovigilance. Of those that reported any involvement in pharmacovigilance (n=117), 49.6% engage in pharmacovigilance activities at a high frequency (once a week or more).

81.9% of respondents agreed ('*Somewhat Agree*' or '*Strongly Agree*') with the statement '*Pharmacovigilance is relevant to my work*' (see **Fig. 26**). Of those that indicated explicit disagreement with this statement (either '*Somewhat Disagree*' or '*Strongly Disagree*'), 66.7% indicated some previous level of involvement in pharmacovigilance activities (between 0-20 years) and 33.3% indicated that they engaged in pharmacovigilance activities more than once a week.

49.0% of respondents had never previously accessed GPV. Of the respondents that had previously accessed GPV (51.0%), 43.0% accessed at a medium frequency (1-3 times a month) and 34.2% at a low frequency (<3 times a year). The most frequently recalled areas of the platform by those that had accessed GPV were 'Training, Education and Careers' (63.3%), 'Home Page' (51.9%) and 'Resources' (44.3%).

92.9% of survey respondents indicated a desire to be kept up to date on the project progression.

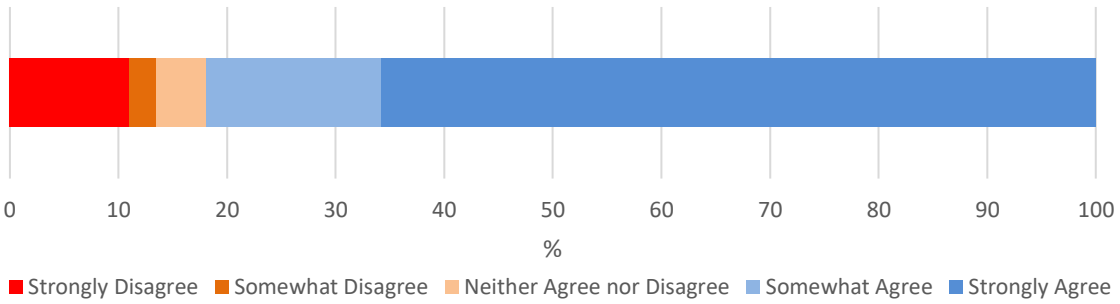


Figure 26: The relevance of pharmacovigilance to pharmacovigilance stakeholders in LRSs. Participants were asked, 'To what extent do you agree with the following statement: Pharmacovigilance is relevant to my work?'

Pharmacovigilance Priorities

Of the pharmacovigilance themes identified in the questionnaire knowledge gap questions, 100% (n=43) achieved a TAF (*'Somewhat Agree' + 'Strongly Agree'*) >75%, and 95.4% (n=41) achieved a TAF >80%. The 10 highest ranked priorities received levels of total agreement between 91.6–94.8% (see **Fig. 27**). A full presentation of the 43 priorities, their ranking, and levels of agreement, can be found in **Appendix 9**.

27.2 Qualitative Results

Free text responses to open-ended questions underwent thematic analysis to identify salient themes. Free text responses were collected for each knowledge-gap question grouping (*'General Vaccine Pharmacovigilance'*, *'COVID-19 Vaccine Pharmacovigilance'*, *'COVID-19 Vaccine*

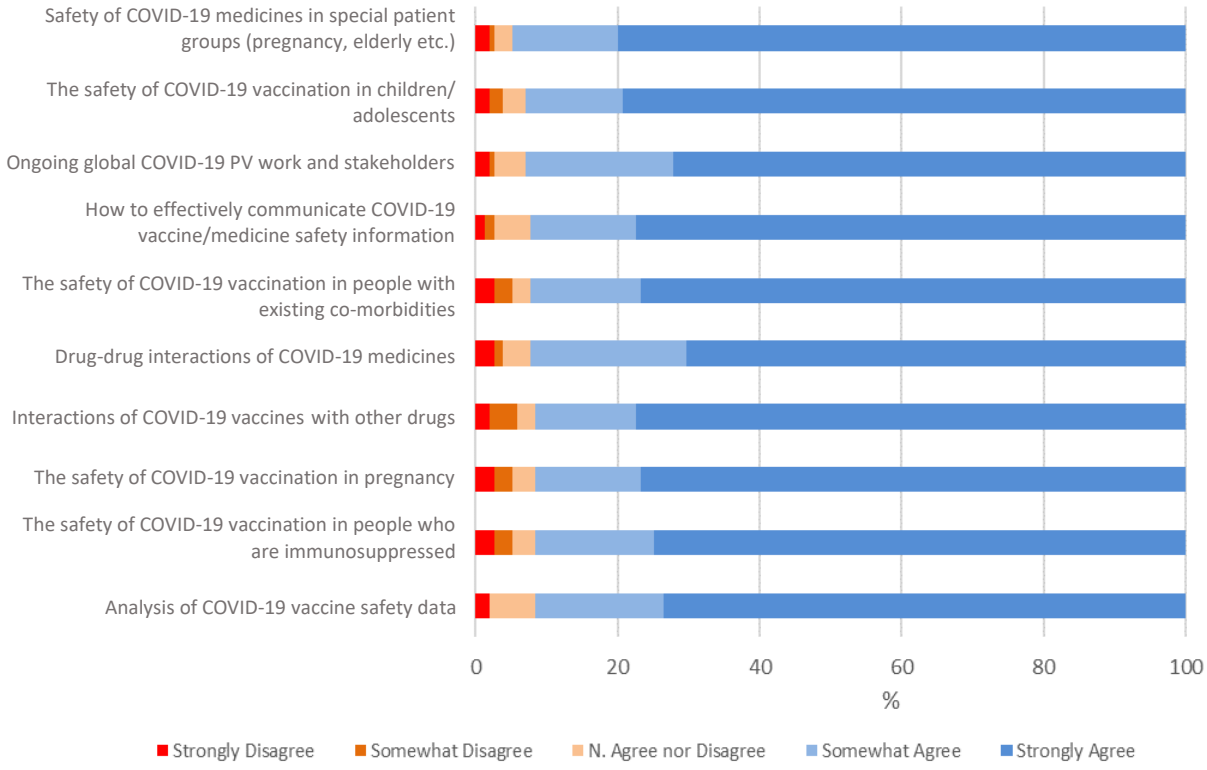


Figure 27: The ten highest-ranked 'pharmacovigilance in LRSs during the COVID-19 Pandemic' themes to which survey participants agreed that they 'needed to know more about'. Themes are ranked in descending order by 'total level of agreement' (% of participants responding either 'Strongly Agree' or 'Somewhat Agree' to the question 'I need to know more about [pharmacovigilance theme]').

Pharmacovigilance According to Patient Group', '*Pharmacovigilance of Medicines Used to Manage COVID-19*', and '*Pharmacovigilance Systems and Communication during the Pandemic*'). Themes and sub-themes identified for each knowledge gap question grouping are presented in **Fig.'s 28** - **32** and overarching themes from the questionnaire are summarised in **Fig. 34**. These themes are examined in-depth in section **28.4**.

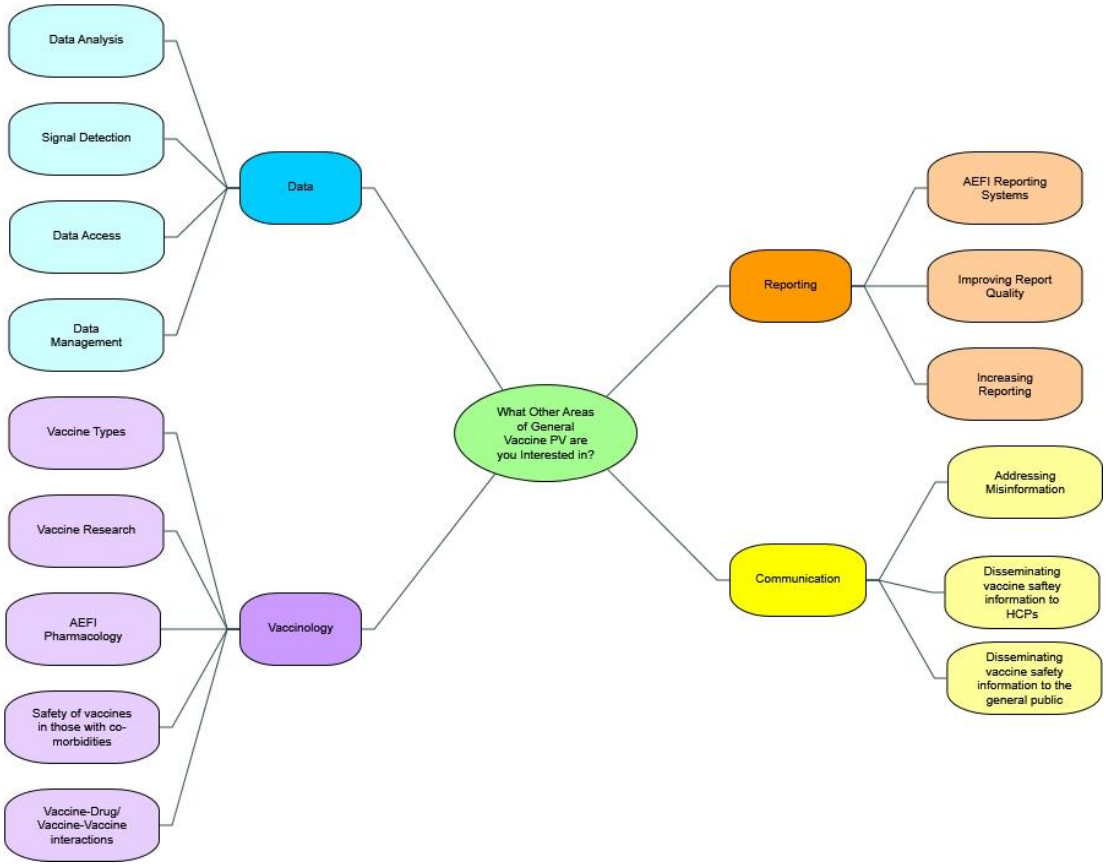


Figure 28: Overview of themes identified from free-text responses to the question 'What other areas of general vaccine PV are you interested in?'. PV = Pharmacovigilance.

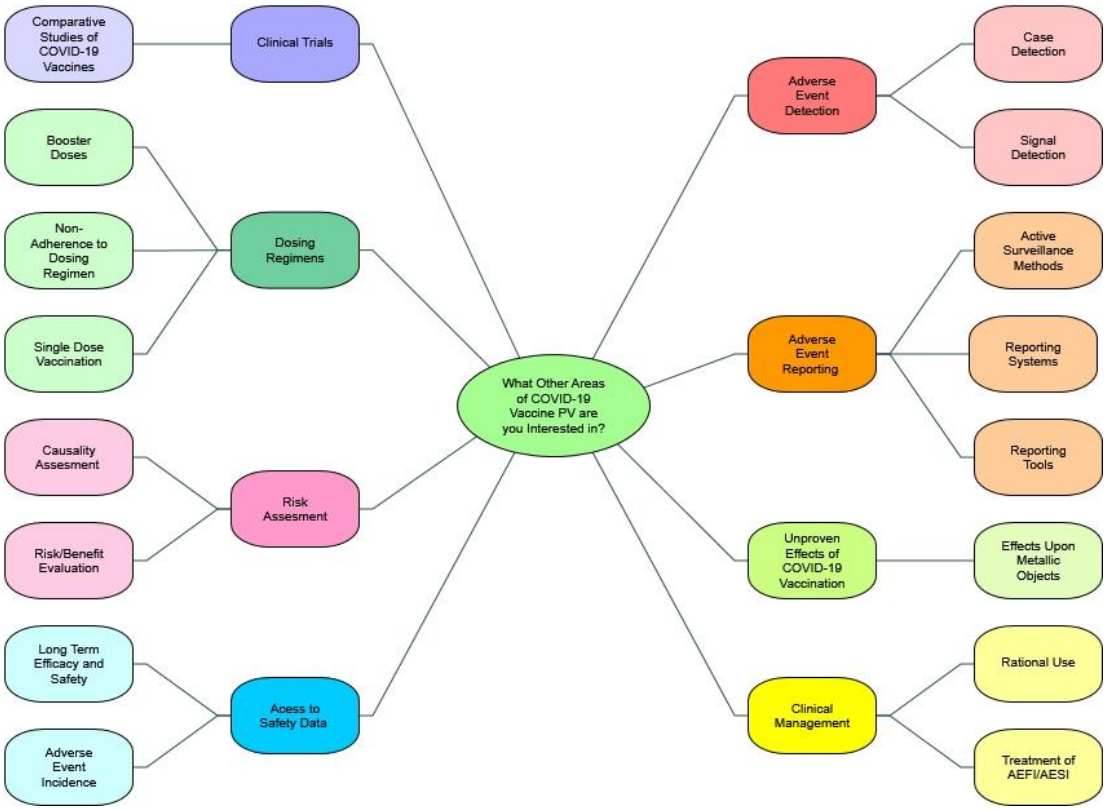


Figure 29: Overview of themes identified from free-text responses to the question 'What other areas of COVID-19 vaccine PV are you interested in?'. PV = Pharmacovigilance.

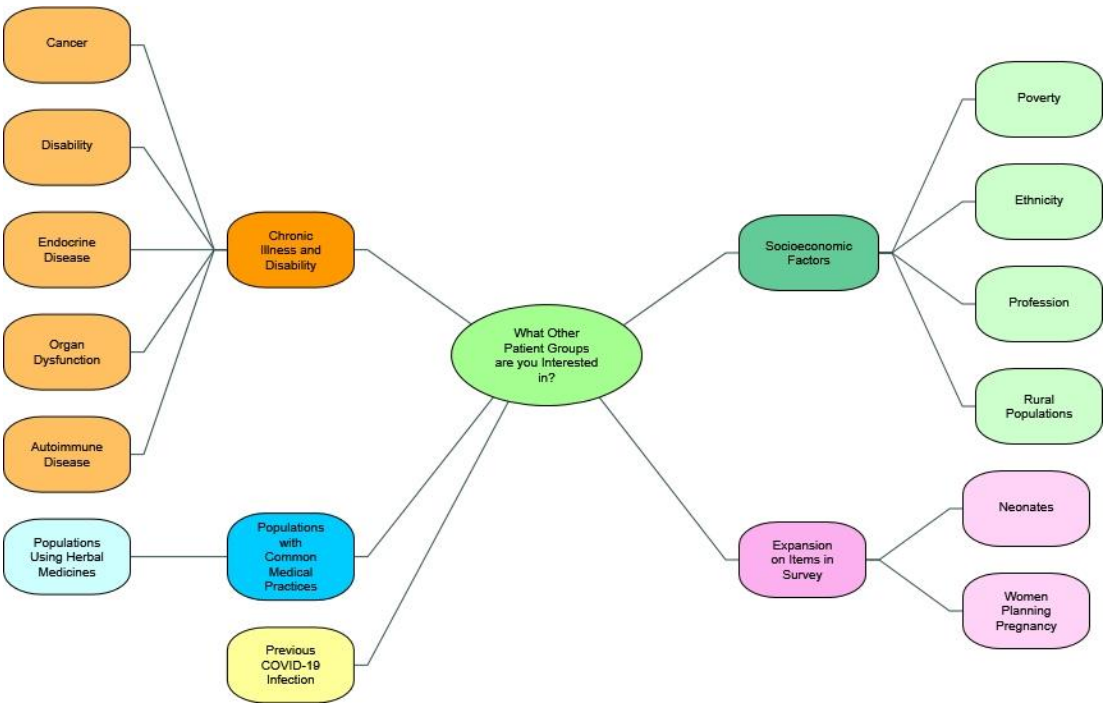


Figure 30: Overview of themes identified from free-text responses to the question 'What other patient groups are you interested in?'. PV = Pharmacovigilance.

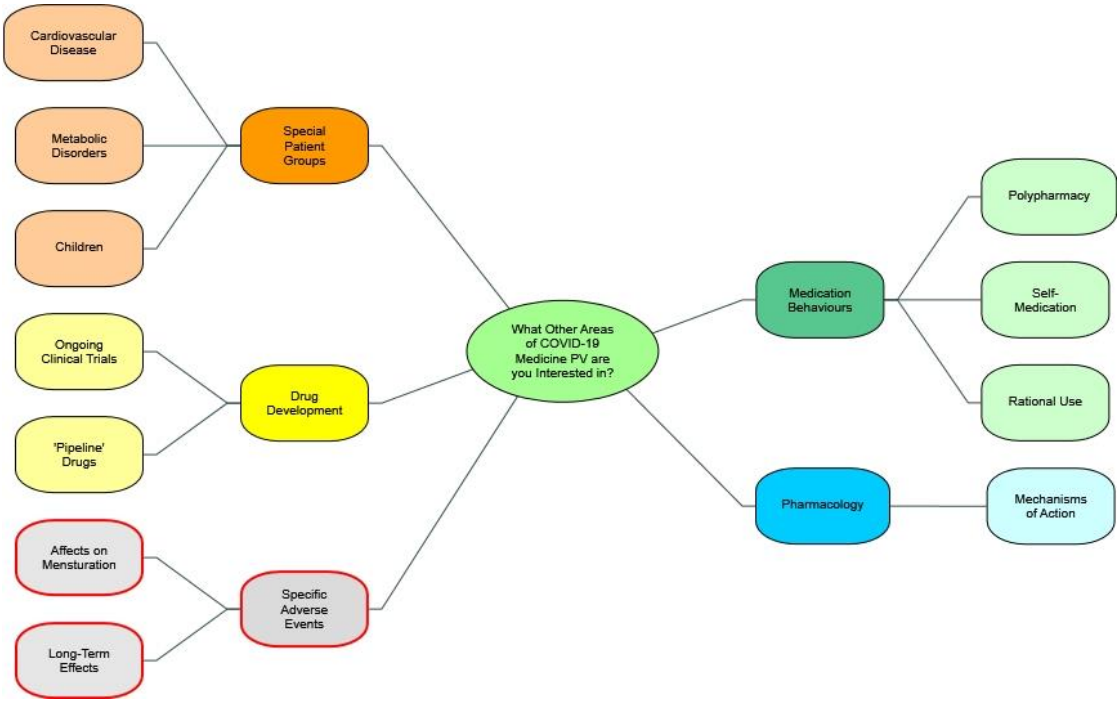


Figure 31: Overview of themes identified from free-text responses to the question 'What other areas of COVID-19 medicine PV are you interested in?'. PV = Pharmacovigilance.

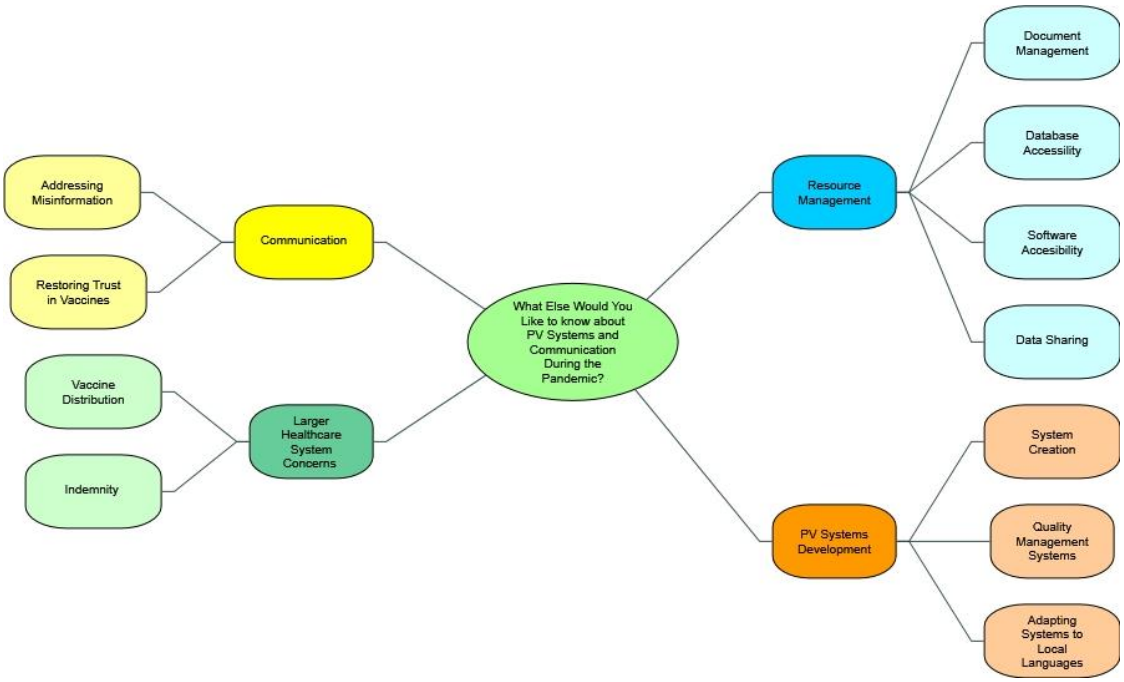


Figure 32: Overview of themes identified from free-text responses to the question 'What else would you like to know about PV systems and communications during the pandemic?'. PV = Pharmacovigilance.

28 Discussion

28.1 Response Rates

The desired minimum response rate (5%) was not achieved. The overall response rate was 2.6%, approximately 50% of the desired minimum. This was despite the extension of the planned survey period by an additional week (see **18.2** and **27**).

The decision to close the survey was made despite these apparently low response rates. Primarily, this was following consideration of the fact that minimum response rate sought (5% of 6000, n=300) had been an overly-ambitious and unrealistic target. This figure was determined following advice from the literature that 5% could be considered an acceptable response rate for online surveys, and from the approximately total membership of GPV at the time of the survey launch (n=~6000).

Determining an accurate size of the pool from which survey participants were being sampled presented several difficulties. Whilst total GPV membership was used to provide a ballpark figure (6000), the actual total of potential participants is likely to have been much lower than this. The total membership figure did not take into account changes in member contact details, members that had opted out of GPV communications, individual member communication habits (checking of email accounts, regularity of social media usage etc) and general interest in/engagement with GPV activities. Moreover, it was impossible to quantify participation of those that were non-GPV members prior to survey participation.

Timescale was an additional consideration in the decision to close the survey early. If the response rate had continued at the same level (approx. 31 responses per week), an additional five weeks would have been required to achieve the 5% target (10 weeks total). Given the aim to rapidly determine the immediate priorities for pharmacovigilance in LRSs, this timeframe was considered unacceptable.

28.2 Demographics

A diverse range of settings and professions were represented amongst the survey participants, the vast majority of whom (85.2%) were based in LMICs. An additional 5.2% of responses (from HIC participants, n=8) demonstrated a clear interest or experience in pharmacovigilance activities in LMICs. It is clear therefore that the survey outcomes were determined primarily by input from LMICs.

Africa was the region with the highest level of survey participation, followed by Asia. It is a logical assumption that survey participation was highly influenced by GPV membership, as Kenya, India, Ghana and Nigeria (four of the five most-represented countries amongst survey participants) were all amongst the 10 LMICs with the highest number of GPV sessions (see **37**). Nevertheless, the overwhelming majority of GPV sessions originating in India did not correlate to an overwhelming majority of Indian survey responses; indeed, more responses were received from Kenya (15.5%) than India (14.8%). The reasons behind this are unknown, although it may indicate that GPV members based in India take a more passive approach to GPV usage (with a greater interest in accessing resources than involvement in research activities), that the high number of GPV sessions originating in India are the result of a much smaller number of individuals repeatedly accessing GPV, or that GPV is being utilised for specific activities in India that are less likely to stimulate involvement in GPV research activities (eg the teaching of undergraduate students regarding pharmacovigilance etc). Lower participation rates were seen from other regions with high numbers of LMICs such as South America, although this is likely to be a result of language barriers. This hypothesis is reinforced by the relative lack of participation from Francophone and Lusophone regions of Africa (see **Fig. 23**).

The variety of professional roles and institutions represented by the participants showcase the diversity of skills, knowledge and expertise that contributed to the survey outcomes. Participation was seen from all of the major 'pharmacovigilance sectors' including academia, the pharmaceutical

industry and regulatory authorities, however the majority of respondents (67.1%) indicated a role as a healthcare professional. In conjunction, 'Hospital' (both public and private) was the most widely represented institution (66.5%), indicating a high-interest in this research and/or pharmacovigilance activities from those with 'front-line', 'patient-facing' clinical roles.

The considerable number of participants who indicated that they held more than one role (44.5%) highlights the multifaceted nature of pharmacovigilance in LMICs. These findings may also reveal a contributing factor to the some of the challenges facing pharmacovigilance in LRSs, such as overburdened workforces, and a lack of dedicated pharmacovigilance staff (see **8.2**). Further investigation is necessary to confirm a causal link between these factors, and determine whether pharmacovigilance stakeholders in LRSs are more likely to hold multiple roles in comparison to their colleagues in HRSs. Regardless, the high level of job sharing suggests a multi-skilled and versatile pharmacovigilance workforce in LRSs.

28.3 Knowledge, Attitudes and Practices

The Scope of Pharmacovigilance

The survey identified a lack of universal agreement regarding the scope of pharmacovigilance amongst pharmacovigilance stakeholders in LMICs. Over 75% of respondents considered the term 'pharmacovigilance' to mean at least '*The detection and assessment of drug-related adverse effects*' (85.2%) or '*Improving the safety, quality and efficacy of all medical interventions including herbal medicines, blood products and vaccines'* (76.1%). However, fewer participants felt that pharmacovigilance included '*The understanding and prevention of drug-related adverse effects'* (67.7%), and only a minority of respondents agreed that pharmacovigilance included '*Encouraging the rational and effective (including cost-effective) use of all medical interventions'* (37.4%).

No participant provided a widely different definition to the WHO pharmacovigilance definition in the free text box included in this question, suggesting that all participants had at least a base-level understanding of the term 'pharmacovigilance'. Additional topics that were considered to fall under the definition of pharmacovigilance included 'communication' ("*Communicating safety issues to relevant stakeholders*"), "*Monitoring medication errors*" and an apparent reference to monitoring the safety of a medicinal product throughout the entirety of its life cycle ("*Throughout the value chain*"). Each of these are consistent with components of pharmacovigilance identified in the literature (see **2**).

The response options included in the question were taken from the WHO definition of pharmacovigilance, and included elements of its expanded scope (see **2**). The results suggest that whilst there is general agreement amongst pharmacovigilance stakeholders in LRSs that the tenets of pharmacovigilance include;

- AE detection
- AE assessment
- Medicines safety
- Medicines quality
- Medicines efficacy
- All medical interventions, including biological products and non-allopathic medicines

There is less agreement that pharmacovigilance concerns:

- Understanding AEs
- Preventing AEs

And little agreement that the following fall under the scope of pharmacovigilance:

- Rational use of medicines
- Effective use of medicines

- Cost-effective use of medicines

Moreover, only a third (34.8%) of all participants selected all of the possible responses, despite each response being a constituent element of the WHO definition/expanded scope. This suggests a poor awareness of the WHO definition of pharmacovigilance and its expanded scope amongst pharmacovigilance stakeholders in LMICs.

In particular, it may be argued that the lower levels of agreement that pharmacovigilance concerns the understanding and prevention of AEs is a surprising result, especially considering that these aspects both feature as components of the WHO core definition of pharmacovigilance (see **2**). The implications behind this finding are uncertain, although it is proposed that a focus of previous pharmacovigilance awareness and training initiatives on the existence of reporting systems and on increasing ICSR generation may have contributed to a perception that pharmacovigilance focuses solely around reporting and data analysis (primarily surveillance activities), but does not extend to activities that act upon safety data. Further investigation of this hypothesis is warranted.

It is possible that the diversity of respondent roles and institutions impacted the variation in opinions regarding the scope of pharmacovigilance. The rational/cost-effective use of medicines for example, may be more likely to be considered a component of pharmacovigilance by policy makers, or those working in healthcare leadership (given that they may be involved in rational use/cost efficacy decisions on a regular basis), compared to an HCP working solely at a ward or clinic level, with little day-to-day exposure to such activities.

Pharmacovigilance Experience

The majority of participants were relatively new to the field of pharmacovigilance (47.7% ≤5 years' experience, 24.5% no involvement in pharmacovigilance at all). This is unsurprising given the relative nascence of pharmacovigilance systems and activities in LMICs, the high turn-over of

pharmacovigilance staff in LMICs reported in the literature (see **8.2**), and the greater likelihood of earlier-career pharmacovigilance stakeholders to seek involvement in a dedicated pharmacovigilance education and training platform such as GPV.

Nevertheless, the considerable number of respondents (24.5%) that indicated no involvement in pharmacovigilance raises the question as to why these individuals participated in in a survey on pharmacovigilance priorities. This raises multiple potential considerations. It may evidence participation due to a general desire to 'begin' the process of learning about pharmacovigilance amongst complete 'newcomers', for example, from the 'Academic/Researcher' (20.5%) and 'Student' (9.1%) responses, the 2nd and 3rd most represented job roles respectively (see **Fig. 24**); This could include academics/researchers from related disciplines looking to broaden their knowledge or engage in pharmacovigilance research for the first time, or students studying pharmacovigilance for the first time. This result may also highlight additional uncertainties regarding the scope of pharmacovigilance (see above), in particular, what constitutes; 'involvement' in pharmacovigilance, pharmacovigilance 'activities', and the individuals that fall within the remit of pharmacovigilance. Frontline HCPs for example, who may feel that they engage in safety-related activities (eg diagnosing, managing, reporting and counselling on ADRs) infrequently, may not consider themselves to have any involvement in pharmacovigilance at all in comparison to a regulator or an individual in the pharmaceutical industry with a dedicated pharmacovigilance role, despite remaining a key stakeholder within the professional pharmacovigilance landscape. Regardless of cause, this finding demonstrates a successful aspect of CoP evolution enabled by the survey; the engagement of pharmacovigilance stakeholders from across the entirety of the pharmacovigilance landscape, regardless of experience, and encompassing individuals that may be underrepresented in previous pharmacovigilance capacity building initiatives. Nonetheless, when considered alongside the above results regarding the technical components of pharmacovigilance, this outcome warrants further investigation into the awareness of the overarching scope of pharmacovigilance amongst stakeholders in LRSs.

Half (49.6%) of those that identified some involvement in pharmacovigilance engaged in pharmacovigilance activities on a minimum weekly basis. This suggests that those participants either held roles dedicated to pharmacovigilance activities (in the case of HCPs, medicines safety experts within their institutions, or involvement in pharmacovigilance work outside of a clinical setting; in this case of academics/researchers, primarily conducting pharmacovigilance-focussed research etc), or that they felt the need to conduct pharmacovigilance activities as part of their daily practice despite not holding dedicated pharmacovigilance roles.

Attitudes towards Pharmacovigilance

The majority of participants (81.9%) felt that pharmacovigilance was relevant to their work. This demonstrates largely positive attitudes to the importance of pharmacovigilance amongst pharmacovigilance stakeholders in LMICs. It is acknowledged that positive attitudes towards pharmacovigilance may be expected amongst a sample drawn from the membership of a dedicated pharmacovigilance platform, and with a potentially high-level of pharmacovigilance-dedicated roles (see above). However, it was noted that amongst those that felt pharmacovigilance was not relevant to their work, two-thirds (66.7%) had some involvement in pharmacovigilance, and one-third (33.3%) engaged in pharmacovigilance activities more than once a week. This demonstrates that that involvement in pharmacovigilance activities cannot be assumed to equate to a positive attitude towards pharmacovigilance.

28.4 Pharmacovigilance Priorities in LMICs during the COVID-19 Pandemic

The universally high levels of agreement (100% of items >75% agreement, 95.4% items >80% agreement, see **Appendix 9**) amongst participants that they needed to know more about all of the pharmacovigilance topics (n=43) included in the survey demonstrates the existence of extensive

COVID-19 pharmacovigilance knowledge gaps amongst pharmacovigilance stakeholders in LRSs. This is further evidenced by the vast amount of additional topics and areas of concern raised by participants in their qualitative responses (see **27.2**). The diversity of the participants (see **27.1**) highlighted that these knowledge gaps existed across the entirety of the pharmacovigilance ecosystem in LRSs worldwide.

Of the 10 highest ranked pharmacovigilance topics, the majority had been grouped in the questionnaire under the theme *'COVID-19 Vaccine Pharmacovigilance According to Patient Group'* (n=4). The remainder were included in the groups '*COVID-19 Vaccine Pharmacovigilance*' (n=2), '*Pharmacovigilance of Medicines Used to Manage COVID-19'* (n=2) and *'Pharmacovigilance Systems and Communication during the Pandemic'* (n=2) (see **Fig. 33**). None of the 10 highest ranked topics were included in the group '*General Vaccine Pharmacovigilance'* (n=2).

These findings demonstrated that keys areas of concern for pharmacovigilance stakeholders in LRSs during the COVID pandemic, where they wished to strengthen their knowledge, primarily surrounded the safety of COVID-19 vaccination in specific patient populations. More specifically, the populations of interest highlighted in the survey results could be described as 'vulnerable' populations. It has been reported elsewhere that these populations often demonstrate lower vaccine uptake, may have sub-optimal responses to vaccines, and in general are routinely excluded from clinical trials [166].

Particular vulnerable groups highlighted in the 10 highest ranked items included "*children/adolescents"*, "*people with existing co-morbidities"*, pregnant women and 'people who are immunosuppressed' (rankings; 2nd, 5th, 8th 9th respectively). The safety of COVID-19 vaccination in vulnerable groups also emerged as a dominant theme in qualitative responses (see **Fig. 34**) with several respondents seeking to offer particular diseases of interest and further expansion on the items in the questionnaire (see **Fig 30**). The majority of these comments focussed on chronic and/or non-communicable diseases, including cancer (eg "*cancer patients*", "*patients on chemotherapy*"),

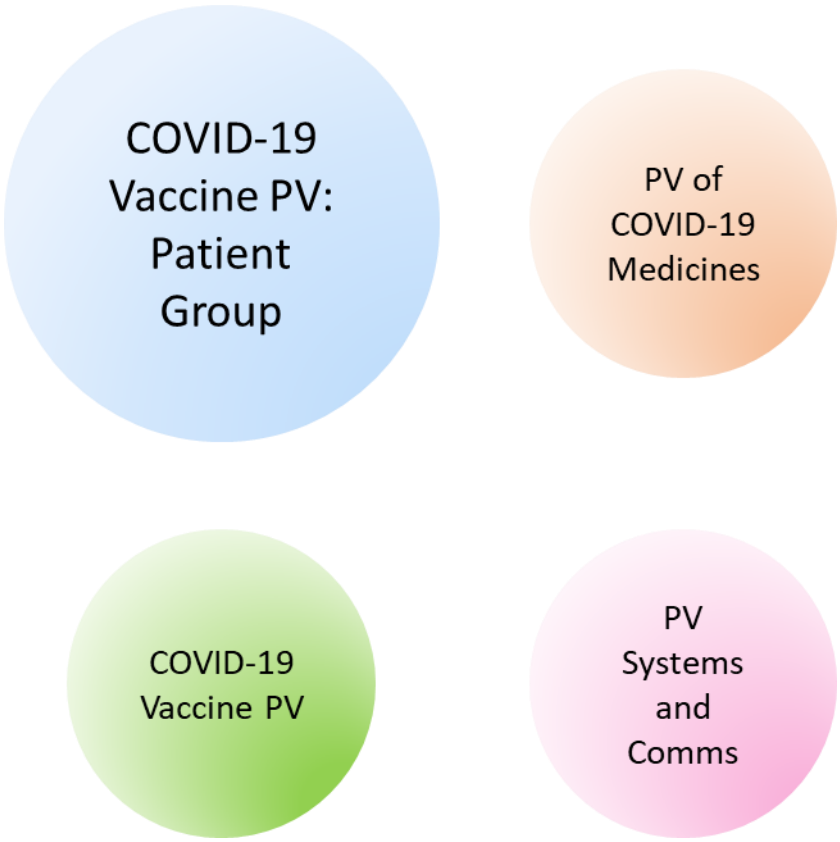


Figure 33: Pharmacovigilance themes represented in the 10 highest ranked pharmacovigilance items. The area of each sphere is proportional to that theme's frequency in the top 10. PV= Pharmacovigilance.

endocrine diseases ("*people with hormonal disorders*"), and those with specific organ dysfunctions ("*patients having organ disfunctioning [sic] like renal and liver disease"*).

Other participants sought to expand on the items relating to maternal and child health, by raising an interest in the safety of COVID-19 vaccination in "*neonates*" and in "*women who are planning to get pregnant*". A particularly novel theme that emerged regarding the safety of COVID-19 vaccination in specific populations was the safety of COVID-19 vaccination in different socioeconomic groups, with participants expressing an interest in how COVID-19 vaccine safety affected "those in "*regions experiencing severe famine*", "*economically affected populations*" and "*rural area communities*". It is proposed that this demonstrates an interest of the safety of COVID-19 vaccination in those whose co-morbidities include diseases of poverty.

The highest-ranked pharmacovigilance topic also concerned vulnerable populations, but specifically concerned the '*safety of COVID-19 medicines in special patient groups (pregnancy/elderly etc)*'. It is possible that a greater interest was noted in pharmacovigilance relating to medicines, as opposed to vaccines, due to the relative infancy of vaccine rollout in LMICs at the time of the survey, and thus a lower local availability of vaccines. The potential impact of questionnaire design on this outcome is also discussed below. Specific vulnerable populations highlighted in qualitative comments included "*cardiac and metabolic disorder patients*" (echoing the interest in chronic/non-communicable diseases seen in regards to COVID-19 vaccine safety described above) and the "*safety of COVID-19 medicines in children*" (echoing the high interest in the safety of COVID-19 vaccine safety in children/adolescents).

Drug-drug and vaccine-drug interactions of COVID-19 medicines/vaccines were another key area of interest (rankings; 6th and 7th respectively). "*Herbal medicine using groups*" were raised as a particular population of interest, and concerns relating to polypharmacy were also highlighted; *"[I need to know more about*] *adverse drug reactions when combining many kinds of medicines*". Some comments regarding specific vulnerable populations, for example, those relating to cancer described above, also appear to indicate an overlapping interest between drug/vaccine-drug interactions and vulnerable groups; the desire to know more about the safety of COVID-19 vaccination in "*patients on chemotherapy*" displays an explicit interest in the pharmacological treatment, as opposed to the disease state.

Further high-ranking areas where greater knowledge was needed included '*Ongoing global COVID-19 pharmacovigilance work and stakeholders*', '*How to effectively communicate COVID-19 vaccine/medicine safety information*', and the '*Analysis of COVID-19 vaccine safety data*' (rankings; 3rd, 4th and 10th respectively).

A general desire to learn more about the contemporary global pharmacovigilance landscape was further evidenced through participant's comments raising interest in a wide-variety of ongoing



Figure 34: Overview of themes relating to pharmacovigilance in LRSs that emerged from free-text responses to all knowledge gap questions.

pharmacovigilance activities, including; clinical trials, "*Drug trials for COVID-19 medications*", "*Comparative study of COVID-19 vaccines*"; AEFI reporting systems "*Case detection and reporting system [sic] for COVID-19 vaccine AEFIs*", "*Assessment of adverse effects and reporting to other global regulators"*; data sharing "*Open access and data sharing on a national, regional and global level on COVID-19 vaccine safety*".

Similarly, the high level of interest in the effective communication of COVID-19 vaccine/medicine safety information was echoed in the emergence of 'communication' as a theme from the survey's qualitative responses (see **Fig. 34**). Comments regarding rumours ("*Rumours during mass*

drug/vaccine administration", "*How to restore trust of the community on covid-19 vaccines after the rumours and myths*") and fake news ("*How to prevent fake news about vaccination*") revealed that tackling vaccine misinformation was of particular interest. Other participants sought to identify specific groups of pharmacovigilance stakeholders with which they wanted to improve communication, specifically 'front-line' HCPS ("*Communicate effectively about the PV protocols to the HCPs from health centres, social workers and other health related stake holders*") and the general public ("*How to disseminate pharmacovigilance results to general public*").

The Analysis of COVID-19 safety data was another topic of interest. Once again, the much broader theme of 'data' emerged as a theme from qualitative responses, of which a constituent sub-theme was data analysis. Specific elements of pharmacovigilance data analysis that were highlighted included signal detection and causality assessment ("*AEFI signal detection and causality assessment*", "*Causality assessment of specific AESI associated with the COVID-19 vaccines*") Related sub themes included data generation, data access and data management.

'Strongly Disagree' responses were received for all pharmacovigilance priority items in the survey (range: n=2-11, 1.3-7.1%). Whilst this represents the minority of total responses, it raises the question as to why any pharmacovigilance stakeholder would suggest that they 'Strongly Disagree' that they need to know more about, for example, the safety of COVID-19 vaccination in pregnancy (see **Fig. 27**). There are multiple solutions that may explain these results. First, these responses may have been received from individuals with extensive experience in the particular fields in question, and who are confident that their knowledge gaps lie elsewhere. Alternatively, the apparent negative extremity of these responses may highlight a flaw in question design; respondents may have selected the 'lowest ranked' scale option to indicate areas of lowest priority, as opposed to topics that they felt they actively did not need to know anything more about (perhaps understandable, given the survey title '*Priorities for Pharmacovigilance…*', The rationale behind question frame design, and its impact on survey outcomes, is discussed elsewhere (see **23.5** and

28.5), but these findings highlight the need for a considered approach to question design in future priority-setting surveys. Regardless of the causative factors, 'Strongly Disagree' responses accounted for only a small minority of total pharmacovigilance priority item responses.

Without further investigation, the applicability of the survey findings to non-COVID-19-related pharmacovigilance in LRSs is unclear. Each of the 10-highest ranked items, discussed above, were 'COVID-19 specific', in that they made specific reference to COVID-19 in the item (eg '*Safety of COVID-19 medicines in special patient groups…*'). Similarly, definitive conclusions cannot be drawn as to whether the findings are applicable to non-COVID-19-related vaccine pharmacovigilance; Indeed, of the five themes used to group knowledge gap questions, 'General Vaccine Pharmacovigilance' was the only theme which was not represented in the 10 highest-ranked items (see **Fig. 27**), and only two out of 10 items from this theme ('*Vaccine Associated Enhanced Disease [VAED]*' and '*Case Definitions of AESIs*', ranked 13th and 17th respectively) ranked in the upper 50% of all pharmacovigilance priorities (see **Appendix 9**). Nevertheless, it is reiterated that all knowledge gap items, including those concerning general vaccine pharmacovigilance, achieved a TAF <75%, indicating significant knowledge gaps across all topics included in the survey. Efforts to reduce knowledge gaps relating to vaccine pharmacovigilance in LRSs would therefore be a welcome step.

However, the fact remains that these systemic knowledge gaps cannot be concluded to correspond to priorities for pharmacovigilance in LRSs outside of the COVID-19 context, without further investigation. Nonetheless, it is proposed that they provide a valuable insight into immediate pharmacovigilance priorities during periods of public health crises, and/or mass drug administration/immunisation, and hence offer a useful guide for targeting funding, research efforts, human resource capacity and training during such dynamic periods of often limited evidence and overstretched resources.

These results provide a much-needed insight into the highest priorities for pharmacovigilance in LRSs during the COVID-19 pandemic. However, the high overall levels of agreement across all survey items, the inter-connectivity of the themes discussed above, the vast amount of additional comments and items for consideration provided by participants and the broad nature of many of the items featured in the survey make it difficult to determine a clear consensus on the most critical priorities.

28.5 Impact of Questionnaire Design on Survey Outcomes

The highest-ranking item of the survey, '*Safety of COVID-19 medicines in special patient groups (pregnancy/elderly etc)*', may have demonstrated a flaw in questionnaire design. As previously discussed, the questionnaire included a group of questions concerning '*COVID-19 Vaccine Pharmacovigilance According to Patient Group*', but did not included a similar group of questions focussed on the pharmacovigilance of *medicines used to manage* COVID-19 (according to patient group). This was noted during questionnaire design and was included as a specific topic for discussion during the debriefing component of the validation process (see **25.5**). No consensus was reached amongst the content experts on the need to include such a group of questions, and only a single item regarding '*the pharmacovigilance of medicines used to manage COVID-19 according to patient group*' was included, in comparison to the six items that made up the '*COVID-19 Vaccine Pharmacovigilance According to Patient Group*' section.

Given the high interest in vulnerable populations demonstrated in the survey, it seems likely that this item achieved the highest ranking as it represents the combination of participants' concerns regarding COVID-19 medicines safety across a range of vulnerable groups (alternative explanations for this items high ranking are discussed above, see **28.4**). If the item had been separated into multiple items (as with the COVID-19 vaccine patient group questions), it is reasonable to assume that the superlative level of agreement would have been 'shared' amongst the constituent items,

thus making it possible for a non-related item to achieve the highest ranking. Furthermore, such separation would have allowed more definitive conclusions to have been drawn regarding particular vulnerable populations of interest. Nevertheless, the high interest in vulnerable populations showcased by the TAF of other items (see **Fig. 27**) suggest that even if this single item had been divided, the constituent items would also have ranked highly amongst the overall priorities.

Another concern discussed in the questionnaire validation process was whether the method of asking the knowledge-gap questions, '*I need to know more about [pharmacovigilance theme]*' provided an accurate measure of pharmacovigilance priorities, given that it assessed participant's subjective opinion of their personal knowledge gaps (see **25.5**). No consensus was reached on a need to amend the question frame by the content experts. Additionally, a potential impact of the discord between identifying 'priorities' and 'knowledge gaps' has been discussed above (see **28.4).**

It is argued that this method of question framing, resulting in the sharing of individual knowledge gaps, demonstrated clear priorities for pharmacovigilance in LRSs during the COVID-19 pandemic where education, training and resources were needed. Whilst the question involved the gathering of subjective opinions on personal knowledge, the personal focus was deemed to be less subjective (and thus a more accurate measure) than alternative approaches requiring participants to propose 'priorities for their country/region'. Although it may be argued that a 'lack of knowledge' does not equate to a 'priority for learning' (a lack of knowledge only equating to a learning priority if the knowledge has immediate and applicable value to the learner), the component of necessity in the question frame ('I *need* to know more about…') indicates that the opportunity to learn more about the items in question was of great importance and value to the participants.

Whether the highest priorities identified in the survey are valuable to national-level policy makers in guiding pharmacovigilance related policy and decisions is unclear, and determining such

priorities was not the aim of this research. Nevertheless, the findings clearly identified priorities for pharmacovigilance education and training in LRSs during the COVID-19 pandemic.

Further justification for this argument was later provided by the workshop results, see **31.1**.

28.6 GPV Usage

Participants were divided in their usage of GPV, as almost half (49.0%) had never previously accessed the platform (see **27.1**). This suggested substantial unfamiliarity with the GPV platform amongst pharmacovigilance stakeholders in LRSs, although this is unsurprising given the relative nascence of GPV and its active engagement activities with its membership on a large scale. Whether those that indicated no previous platform access were new members that had registered with the platform as part of their participation in the survey, whether they were longer-standing TGHN members that had used other TGHN platforms but not GPV, or whether they were longer-standing GPV members that had not accessed that platform since their registration, was not assessed. Regardless, it is clear that the survey stimulated considerable novel engagement in GPV's activities.

Those that did access GPV were most likely to do so at a medium or low frequency (from 3 times a month to <2 times a year). This offers potential insight into GPV user-ship habits, which suggest that, as opposed to using GPV to support day-to-day pharmacovigilance activities on a regular basis (eg to support daily data analysis in a pharmacovigilance centre, regular study activities etc) users access GPV to support less infrequent pharmacovigilance activities (eg periodic training, careers insights, etc)

The most frequently accessed components of GPV, as recalled by participants, were 'Training, Education and Careers', followed by the Home Page, and 'Resources'. This provides further clarification of motivation for using GPV, which appear to primarily concern gaining access to

training and education materials, gaining access to support the conduct of pharmacovigilance activities, and to seek support in the advancement of a pharmacovigilance career.

29 Conclusion

Extensive knowledge gaps regarding COVID-19-related pharmacovigilance exist amongst pharmacovigilance stakeholders in LMICs. There is an urgent need for initiatives to address these gaps, and reduce the risk of COVID-19 vaccine/therapeutics harm to populations in these settings.

These results provide a much-needed insight into the highest priorities for pharmacovigilance in LRSs during the COVID-19 pandemic. However, the high overall levels of interest across all survey items, the inter-connectivity of the themes discussed, the vast number of additional comments/items for consideration provided by participants and the broad nature of many of the items featured in the survey make it difficult to determine a clear consensus on the most critical priorities. Nevertheless, the highest-ranking topics identified in this survey provided an excellent guide for further research in this area.

Future research should focus on the themes of COVID-19 vaccination safety in vulnerable populations, COVID-19 vaccine/drug-drug interactions, global COVID-19 pharmacovigilance work, the communication of COVID-19 vaccine/therapeutics safety information and the analysis of COVID-19 vaccine safety data. Investigations should seek to achieve a clear consensus on the highest immediate priorities amongst these themes, and further elucidate the precise challenges and bottlenecks within them.

Awareness of the full scope of the field of pharmacovigilance is limited in LMICs. Education and sensitisation efforts seeking to increase the understanding and awareness of pharmacovigilance activities in LMICs should be sure to include discussion of the entire spectrum of pharmacovigilance

operations. Highlighting how pharmacovigilance can encompass the rational and cost-effective use of medicinal products is recommended.

VI Workshop

Following completion of the survey, and the high level of agreement on the need for participants to know more about all aspects of pharmacovigilance in LRSs assessed therein, it was decided that a further open, and preferably interactive, consensus building activity was needed to clearly define the immediate priorities for pharmacovigilance in LRSs. A comprehensive overview of the workshop methodology (see **19**) has been provided previously. The component stages of the research cycle were met as follows:

- **Plan:** Need for further consensus building activities identified following reflection upon survey results, workshop strategy planned (see **19.1**).
- **Act:** Potential workshop chair(s) identified and engaged, workshop promoted, supportive documents developed (see **19.2**, **19.3** and **Appendix 10**).
- **Observe:** Workshop and workshop polls conducted (see **19.4** and **19.5**).
- **Reflect:** Considered workshop findings, their implications for pharmacovigilance in LRSs, and whether clear priorities had been identified (see below).

For a visual representation of the validation methods applied to the action research cycle, see **Fig. 35**.

30 Workshop Objectives

- To present the findings of the survey to the CoP.
- To facilitate discussion of the highest pharmacovigilance priorities identified by the CoP, their relevance to the CoP member's setting, and to elucidate further information on the precise aspects of these priorities that are areas of concern.
- To gather further consensus on the CoP's top priorities for pharmacovigilance.

- To provide an overview of GPV to the CoP.
- To communicate the intention to form working groups to address the top-rated priorities identified in the workshop.

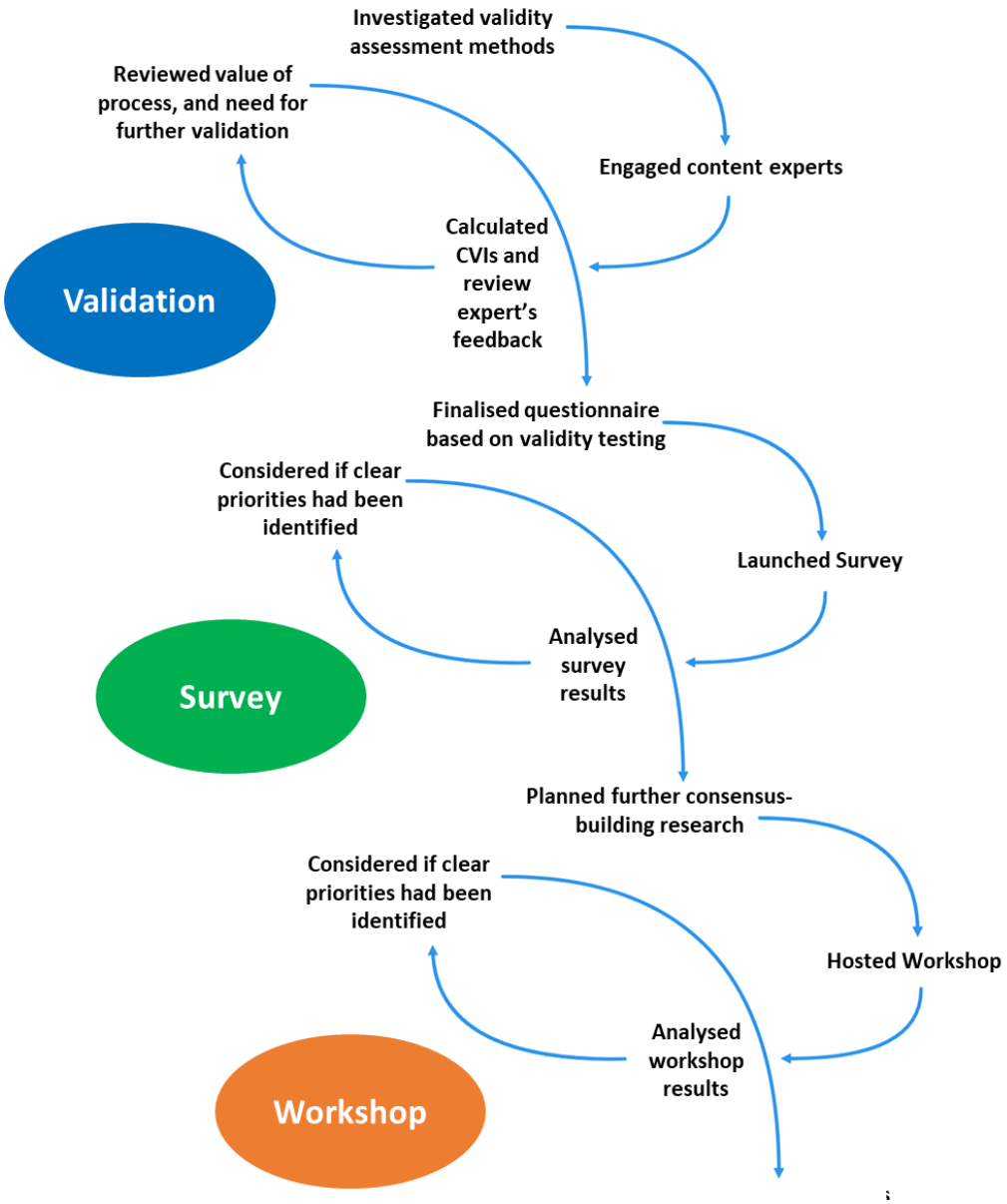


Figure 35: Workshop methodology within the action research cycle. Having been informed by the outcomes of both the validation and the survey, the iterative process continues. Adapted from **Fig. 10**.

31 Results

The open workshop was held on 10th Feb 2022, 13.00-15.00 GMT. The chairing panel consisted of the four members of the ISoP Africa Chapter Executive Committee (EC) 2019-2022 (see **8.2**). In addition, two project researchers gave presentations. Both the project researchers and chairing panel provided responses to attendee questions. 553 participants registered to attend the workshop, with 257 (46.5%) attending the event.

31.1 Quantitative Results

Workshop: Demographics

257 individuals from 61 countries attended the workshop (see **Fig. 36.A**). This included 41 LMICs (67.2%) and 20 HICs (32.8%). 78.2% of all attendees (n=201) were based in LMICs. Over half of all attendees (56.4%) were based in Africa, with Asia being the second most represented region (14.8%). The countries most represented were Kenya (21.4%), the US (7.0%), Nigeria (6.2%), India (6.2%) and Ghana (5.8%).

21.8% of attendees were apparently based in HICs, primarily the US (7.0%) and the UK (5.4%). During analysis (see **32.1**), it was realised that these findings were influenced by the usage of Virtual Private Networks (VPNs) by some individuals based in LMICs, and that actual HIC attendance was therefore lower than appeared. The number of workshop attendees using VPNs could not be determined. Nevertheless, this indicates that the percentage of workshop attendees based in LMICs was likely to be >78.2%.

The most represented profession amongst all workshop attendees was pharmacist (17.7%), followed by 'Academic/Researcher' (11.8%), 'Student' (8.0%) and 'Pharmacovigilance Leadership (Industry)' (7.6%) (see **Fig. 37.A**). 23.6% of all attendee's job roles were unable to be definitively

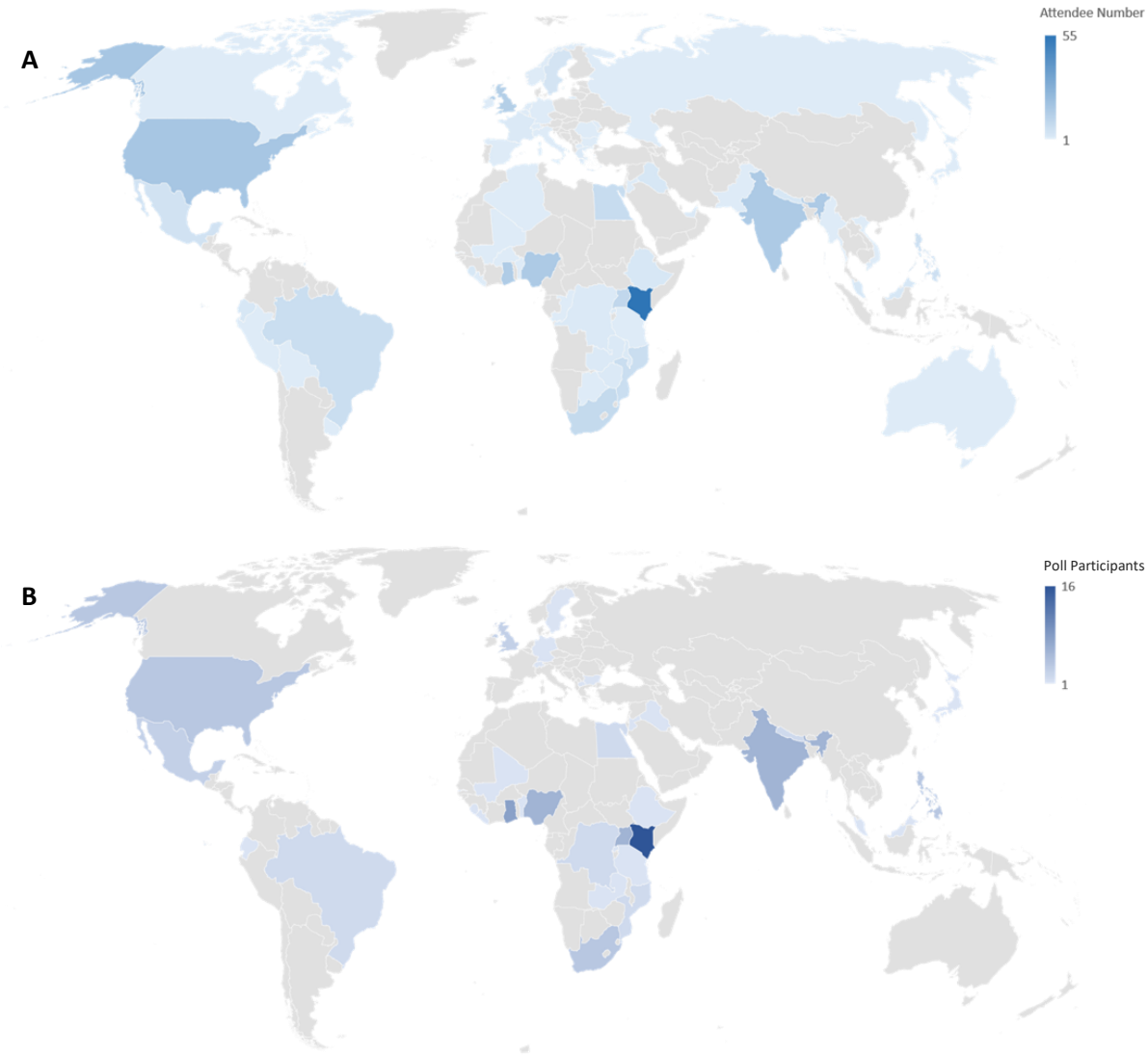


Figure 36: Countries represented by (A) workshop attendees and (B) poll participants. Not visible at this scale is Trinidad and Tobago (1 Attendee [A], 1 Poll Participant [B]). The high proportion of attendees (A) identified as representing the US, and to a lesser extent the UK, was later realised to be in part due to the usage of Virtual Private Networks (VPNs, see **32.1**).

grouped or classified. The most represented institutions amongst all workshop attendees were 'University/College' (21.8%), 'Ministry of Health' (10.5%), 'Hospital' (10.1%) and 'Consultancy' (7.8%) (see **Fig. 37.B**) 9.7% of all institutions represented by attendees were unable to be classified.

63.4% (n=163) of attendees attended the workshop for at least 50% of the workshop's allotted time (60 mins) and 47.0% (n=121) of attendees attended the workshop for at least 75% of the workshop's allotted time (90 mins). Of those that attended the workshop for at least 75% of the

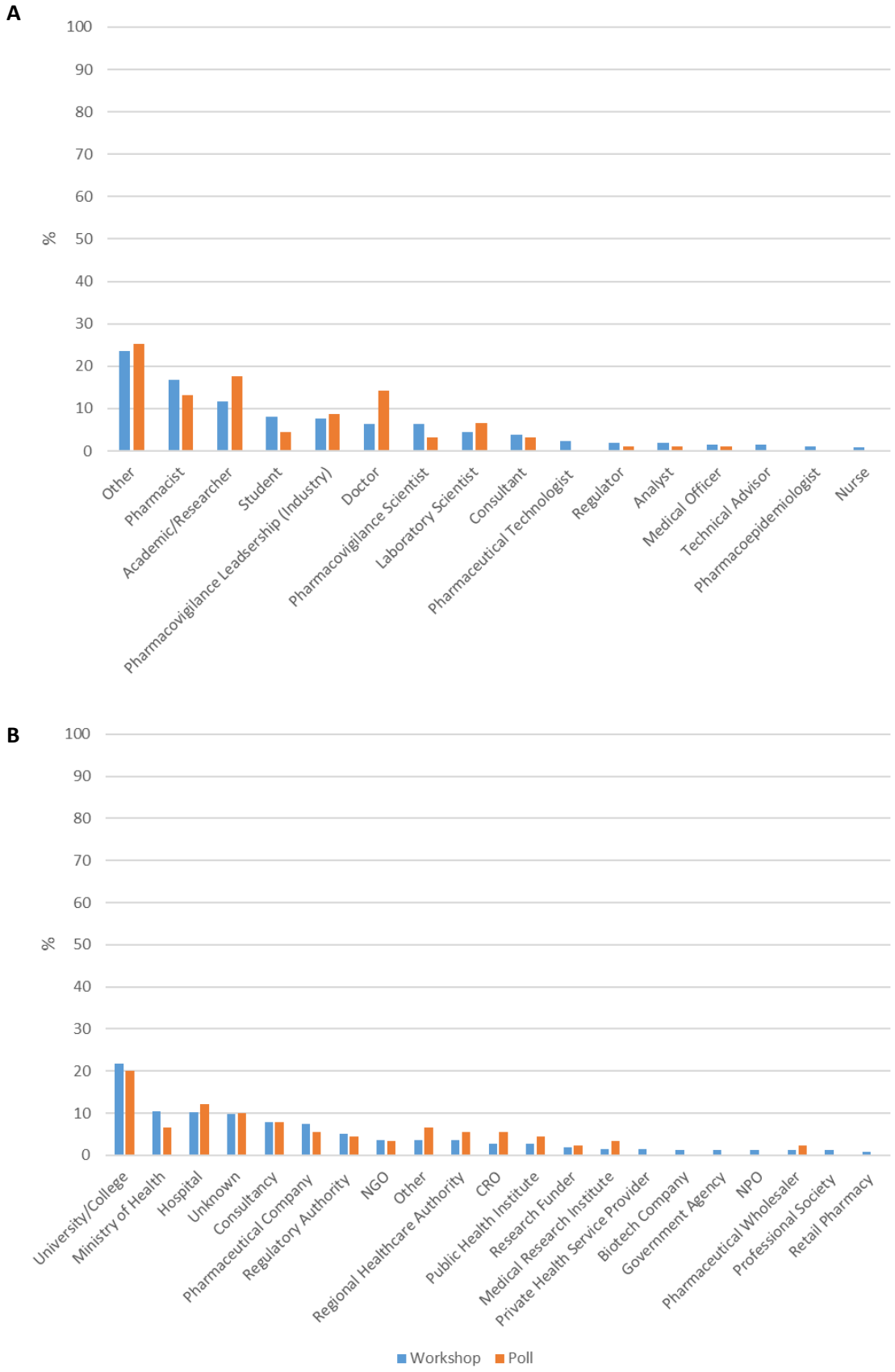


Figure 37: Job roles (A) and institutions (B) of workshop attendees and poll respondents. Note that 9.7% of workshop attendee's institutions (A) and 10.0% of poll respondent's institutions (B) could not be identified and so were grouped as 'unknown'. Job roles and institutions that were clearly identifiable, but that could not be definitively classified were grouped as 'other'.

allotted time, 76.9% were based in LMICs (HICs; 23.1%). 3.9% of attendees (n=10) provided their demographic information (job role and institution) in a language other than English (Spanish n=8; French n=2).

Poll: Demographics

90 workshop poll responses were received; 82 (91.1%) 'in-workshop' and eight (8.9%) 'post-workshop'. 35 countries were represented by the poll respondents (see **Fig. 36.B**), including 28 LMICs (80.0%) and seven HICs (20.0%). 86.7% (n=78) of individual responses were received from respondents based in LMICs (HICs; 13.3%, n=12). The countries most represented were Kenya (17.8%), Ghana (8.9%), India (6.7%), Nigeria (6.7%) and Uganda (6.7%).

Priority	Total Votes	Ranking
The safety of COVID-19 vaccination in pregnancy	43	=1
The safety of COVID-19 vaccination in children/adolescents	43	=1
Analysis of COVID-19 vaccine safety data	40	3
The safety of COVID-19 vaccination in people with existing co-morbidities	35	4
How to effectively communicate COVID-19 vaccine/medicine safety information	31	5
Interactions of COVID-19 vaccines with other drugs	27	=6
The safety of COVID-19 medicines in special patient groups (pregnancy, elderly, etc)	27	=6
The safety of COVID-19 vaccination in people who are immunosuppressed	22	8
Ongoing global COVID-19 PV work and stakeholders	12	=9
Drug-drug interactions of COVID-19 medicines	12	=9

Table 12: Ranking of pharmacovigilance priorities in LRSs during the COVID-19 pandemic.

The most represented profession amongst poll respondents was 'Academic/Researcher' (17.6%), followed by 'Doctor' (14.3%), 'Pharmacist' (13.2%) and 'Pharmacovigilance Leadership (Industry)' (8.8%) (see **Fig. 37.A**). 25.3% of all poll respondent's job roles were unable to be definitively grouped or classified. The most represented institutions amongst all poll respondents were 'University/College' (20.0%), 'Hospital' (12.2%), 'Consultancy' (7.8%) and 'Ministry of Health' (6.7%) (see **Fig. 37.B**). 10% of all institutions represented by poll respondents were unable to be classified.

Poll: Pharmacovigilance Priorities

The final ranking of the pharmacovigilance priorities presented in the workshop is shown in **Table 12.**

Poll: In-Workshop Pharmacovigilance Priority Response Numbers

84.1% of in-workshop poll respondents (n=69) provided the requested number of responses (3) to the pharmacovigilance priority question. The individual number of responses provided ranged from 1-9. The average number of responses provided per person was 3.27.

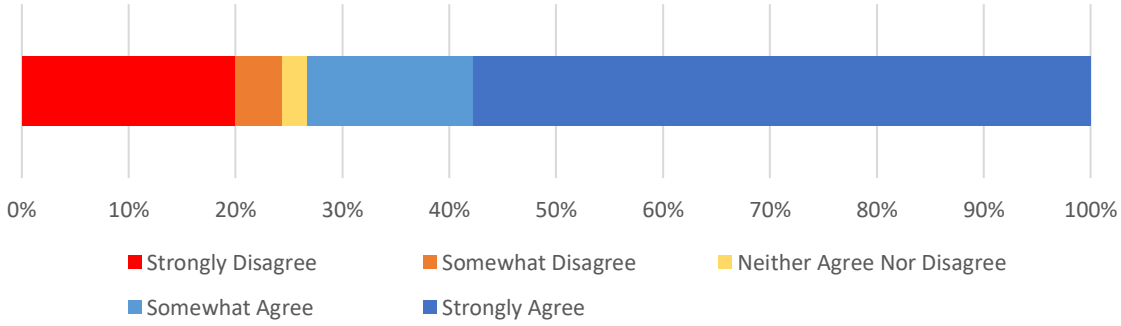


Figure 38: Did workshop participants feel that the 10 highest pharmacovigilance priorities identified in the survey remained relevant to their setting at the time of the workshop? Combined data for in- and post-workshop polls. Time period between survey closure and workshop = 115 days. Strongly Agree = 57.8%; Somewhat Agree = 15.6%; Neither Agree nor Disagree = 2.2%; Somewhat Disagree = 4.4%; Strongly Disagree = 20.0%.

Poll: Priority Relevance

The majority (73.3%) of all poll respondents (both in- and post-workshop) agreed that the 10 highest pharmacovigilance priorities identified in the survey and then presented in the workshop remained relevant to their setting at the time of the workshop (see **Fig. 38**).

Theme	Code	Sub-Code
Collaboration	Lack of collaboration	
	Collaboration is important	
	Engaging all stakeholders	
	Sharing the resource burden	
	Current PV collaborations in LMICs	PAVIA [167] PROFORMA [168] AMRH (see **8.2**)
Communication	Lack of communication	
	Lack of feedback	
	Patients not given vaccine information	
COVID-19 as an Opportunity	Improved awareness of reporting tools	
	Increased numbers of AEFI reports	
	Improved online communications	
	Extending work beyond the pandemic	
Data	Data collection is inadequate	Obtaining follow-up information is challenging Paper-based reporting systems need upgrading
	Existing Reporting Tools in LMICs	Med Safety App National Reporting systems PViMS VigiFlow
	Active Surveillance Activities	
	Data from Specific Populations	Leveraging existing safety studies
Information	Signposting to information sources	
	Reliable Information	
Research	Ongoing PV Research in LMICs	
	Lack of Research	
	Need for research into COVID-19 Vaccine safety in pregnancy in LMICs	
Support	Greater support needed for PV activities in LMICs	Active surveillance Resources Overburdened HCPs
Africa		
Feedback	Presentation and Research Workshop	
Further Involvement		

Table 13: Themes, codes and sub-codes that emerged in the open workshop. Themes related to both pharmacovigilance in LRSs (see **Fig. 33**), and the project research activities. PV = Pharmacovigilance.

31.2 Qualitative Results

The survey discussion, and written Q&A and chat comments underwent thematic analysis to identify the themes that emerged in the workshop. An overview of all themes identified and relevant codes are shown in **Table 13**, and themes specific to pharmacovigilance are summarised in **Fig. 39** and discussed at length below (see **32.6**).

32 Discussion

32.1 Demographics

As encountered with the survey, a diverse range of settings and professions were represented amongst the workshop attendees and poll respondents.

The majority of attendees (78.2%) were based in LMICs, as were an even greater proportion of poll respondents (80.0%). However, a large number of attendees were noted from the US (n=18, 2nd highest number of attendees) and the UK (n=14, 6th highest number of attendees). During analysis, this was realised to be in part due to the usage of Virtual Private Networks (VPNs) by some attendees, providing US or UK Internet Protocol (IP) addresses for attendees that in actuality were based elsewhere. Zoom generates attendee geographic data based on an attendee's IP address, and so it was realised that several of the attendees listed as being based in HICs were actually based in LMICs and utilising a VPN. The percentage of workshop attendees based in LMICs was therefore likely to be >78.2%.

Despite these inaccuracies, it is clear that the workshop discussions and poll outcomes were led by primarily by participants from LMICs. In addition, the high numbers of attendance from some individual HICs described above did not translate to similar high levels of poll responses from those countries. This demonstrates the successful communication of the poll aims, scope, and target audience during the workshop.

As with the survey, Africa and Asia were the regions most represented by participants, whereas lower participation was noted from other regions with high proportions of LMICs (eg South America, Central America, The Caribbean and Oceania). Whilst similar conclusions can be drawn for these outcomes as with the survey (language, GPV usage etc, see **28.2**), this is likely further compounded by the 'real-time' nature of the workshop; Regions with smaller time-differences to the workshop (held 13.00 BST) appeared better represented (ie time zone range across mainland Africa; BST+2 [EAT, eg Kenya] - BST-1 [GMT, eg Ghana], as opposed to time zone range across mainland South America; BST-4 [BRT, eg Brazil] - BST-6 [eg COT, Colombia]).

Paralleling the survey results, participants held a wide range of job roles and represented a diverse range of institutions (see **Fig. 37**). In comparison to the survey, and as a result of the different methods employed to collect demographic data (see **32.2**), a wider number of specific institution types and job roles were identified in the workshop (job roles: 15, institutions: 19) than in the survey (job roles: 12, institutions: 16). This expansion provided further insight into the diversity of skills and knowledge held by pharmacovigilance stakeholders in LRSs. Nevertheless, many job roles could not be categorized definitely, and a considerable proportion of institutions could not be identified at all. A more detailed explanation of these outcomes can be found below. Despite these difficulties, it is apparent that the workshop discussions and poll outcomes were led by a diverse population of pharmacovigilance stakeholders with varied skillsets, knowledge bases and professional perspectives.

32.2 Difficulties in Defining Job Roles and Institutions

Unlike the survey, in which participant job roles and institutions were determined using closed, multiple-choice questions featuring a predetermined list of response options, information regarding workshop participant job roles/institutions was gathered via open-ended, free text

responses. This was due to the restrictions of the workshop software registration form that was used to gather demographic data.

This presented a number of challenges to the researchers. In order to effectively analyse the data, it became necessary to code the free text responses. Responses were coded using the response options provided to the job role/institutions questions in the survey, the Institute of Pharmacovigilance/ISoP Pharmacovigilance Career Framework Guideline, and via the emergence of additional codes from the data. [169].

In many incidences (and particularly in relation to non-clinical roles) precise job roles could not immediately be identified from the job titles provided. Coding institutions via institution name was an even more difficult task. In both cases, internet searches (Google) to precisely determine job role and institution classifications were conducted on an individual basis.

Given the large number of workshop attendees, this was a considerably time-consuming process, and even following the internet searches, roles/institutions could not always be definitively classified. This is reflected in the high number of job roles classified as 'Other' and the high number of institution types classified as 'Unknown' or 'Other'[*].

Notwithstanding these complications, the enormous variety of job roles and institutions represented by workshop participants (n=257) showcases the tremendous professional diversity and range of skills and knowledge amongst pharmacovigilance stakeholders in LRSs. The wide variation in the responses received highlighted both the vast number of roles within the pharmacovigilance environment, but also the heterogeneity of job titles for similar pharmacovigilance roles, particularly within the pharmaceutical industry. This only serves to

[*] The term 'Other' is used to classify roles/institutions that were identifiable, but could not be grouped definitively amongst the codes established. The term 'Unknown' (used only to describe institutions) is used to group institutions that could not be identified from the participant's description, or a subsequent internet search.

underscore the importance of initiatives seeking to clarify and promote standardisation of job role terminology in the pharmacovigilance sector.

It is recommended that researchers looking to gather professional demographic information from diverse groups of pharmacovigilance stakeholders use close-ended, multiple choice questions, with response options limited to 'sectors' ('Pharmaceutical Industry', 'Medicines Regulation', 'Academia' etc) to facilitate data collection and analysis. It is envisaged that such response options will provide an appropriate level of insight into the target population, and allow further investigation if necessary.

32.3 Priorities for Pharmacovigilance in LMICS during the COVID-19 Pandemic

The three-highest priorities for pharmacovigilance during the COVID-19 pandemic where support, training and guidance were needed (Feb 2022) were '*The safety of COVID-19 vaccination in pregnancy*' (ranking: =1st) '*The safety of COVID-19 vaccination in children/adolescents*' (ranking: =1st), '*Analysis of COVID-19 vaccine safety data*' (ranking: 3rd) (see **Table 12**).

The high level of interest in maternal and child vaccine safety echoes the concerns regarding COVID-19 vaccine safety in vulnerable populations identified in the survey (see **28.4**), and provides further insight into the vulnerable populations of greatest interest. Strong interest in these particular populations amongst pharmacovigilance stakeholders in LRSs is understandable, given that globally, the highest fertility rates, highest birth rates, highest maternal mortality rates, highest infant mortality rates, and lowest median ages are generally seen in LMICs.

These findings were further substantiated by comments made by the Chairs in the workshop discussion, which highlighted a lack of local research into the safety of COVID-19 vaccination in pregnant women:

> **"***Some countries I know, even in Uganda, are specifically studying [the] safety of vaccines in pregnancy, but I don't know whether this has been applicable to COVID-19. I've not heard about safety of COVID-19 vaccines in pregnancy*"
>
> **Chair #1, ISoP Africa Chapter EC**

> "*[Regarding the safety of COVID-19 vaccine in pregnancy] I haven't at the moment seen a lot of papers coming out from LMIC countries, but I do know that there are quite a number of studies – data that has been collected in other parts of the world, that have shown to a large extent that there aren't any serious risks… and I think that is really one area that we could also focus on in LMICs, to get that kind of real-world data in what's happening*"
>
> **Chair #2, ISoP Africa Chapter EC**

In addition, specific questions and requests for further information were raised by workshop participants regarding the safety of COVID-19 vaccination during pregnancy and breastfeeding:

> "*Do we have information on the safety of COVID-19 vaccine [sic] on nursing mothers, especially on breast feeding?*"
>
> **Research Officer, University, Nigeria**

Medical intervention safety in pregnant women and children has historically been a topic of great sensitivity. Widespread public sensitisation to medicines-related risks in these groups, driven by extensive mass media coverage of historic medicines safety tragedies and scandals (most famously, the use of thalidomide in pregnancy and its teratogenic effects, but more recent LRS examples include DEG-contaminated medicines, (see **2.1** and **8.1**) is likely to contribute to high levels of underlying concern regarding COVID-19 vaccination safety in these populations.

As previously described (see **28.4**), pregnant women and children are often systematically excluded from clinical trials. Whilst, increasingly, these populations have begun to see inclusion in both COVID-19 therapeutic drug and vaccine trials (including trials with participation in LRSs, eg WHO Solidarity PLUS trial [170]), such inclusions remain outside the norm, and there have been repeated calls amongst the scientific community to increase the participation of pregnant women and children in such trials [171, 172]. Despite these efforts, an awareness of the historic exclusions from

clinical trials is likely to contribute to uncertainties regarding the safety of novel medical interventions such as the COVID-19 vaccines in pregnant women and children/adolescents.

In comparison to the survey, priorities that focused solely on the safety of COVID-19 medicines generally ranked lower than priorities that focused on vaccines (eg '*The safety of COVID-19 medicines in special patient groups [pregnancy, elderly, etc]*', highest ranked priority in the survey, dropped five places following the workshop ranking). It is proposed that this reflects the expansion of COVID-19 vaccine rollouts in LMICs and increase global vaccine coverage between the conduction of the survey and the workshop, and hence an increased interest in vaccine, as opposed to medicines, safety.

A strong desire to know more about the analysis of COVID-19 safety data was also of high interest to the workshop participants. This reflects concerns regarding pharmacovigilance data that emerged in the survey (see **28.4**) and in the survey validation process (see **Appendix 7**). Whilst data 'analysis' was highlighted as a particular priority via the quantitative methods in the workshop much of the qualitative data focussed on the need to increase data generation and improve data access in LRSs.

The themes of 'data analysis' and 'data access' represent two distinct but highly interdependent topics within the overarching theme of 'data', that emerged from the survey and workshop's results; clearly, data analysis cannot take place if data is unavailable.

The '*Analysis of COVID-19 vaccine safety data*' item ranked considerably higher in the workshop poll than it did in the survey (rankings 3rd and 10th, respectively). In a similar fashion to the increased interest in vaccines over medicines described above, it is suggested that the increased interest in COVID-19 vaccine data analysis between the conduction of the survey and the workshop was driven by the expansion of the COVID-19 vaccine rollouts in LMICs in this period; Greater vaccine coverage likely resulted in an increase in AE reports, and thus an increased need to conduct data analysis.

Despite the similarities in these scores, '*How to access COVID-19 vaccine/medicine safety data'* was not included in presentation of the 10 highest-ranked survey items during the workshop. This was due to the fact that survey items rankings were ranked systematically, primarily by TAF, and in the case of joint rankings (as described here), by the item with the highest 'Strongly Agree' score, then by 'Somewhat Agree' scores, and so on. Both the '*Analysis of COVID-19 vaccine safety data*' and '*How to access COVID-19 vaccine/medicine safety data*' items demonstrated very similar levels of agreement; A definitive ranking was only determined due to of greater number of 'neither agree nor disagree' responses to the data analysis item, as opposed to the data access item (n=10 vs n=8, see **Appendix 9**). In addition, the workshop software polling functions only allowed for the inclusion of 10 response options; it was therefore impossible to include an 11th response option, no matter how close the total agreement scores, when using the workshop software adopted.

As previously discussed, the topic '*How to access COVID-19 vaccine/medicine safety data*" featured as a questionnaire item in the survey, and received the same TAF as the item '*Analysis of COVID-19 vaccine safety data*', making it the =10th highest-ranked survey item (see above and **Appendix 9**). This demonstrates a high level of interest in the concurrent themes of data analysis and data access throughout both consensus-gathering activities.

32.4 Priority Relevance

Given that the workshop took place four months after the conclusion of the survey, and considering the speed of public health developments across the globe during that stage of the pandemic (Oct 2021- Feb 2022), it was deemed necessary to determine 'in-workshop' as to whether the highest priorities identified in the survey (and hence, those presented in the workshop) remained relevant to the participants' settings. A question was included in the workshop poll to test this consideration (see **Fig. 38** and **Appendix 11**).

The majority (73.3%) of all poll respondents agreed that the pharmacovigilance priorities presented in the workshop remained relevant to their setting. These results were reinforced by comments received during the workshop discussion prior to the conduction of the poll:

> "*These priorities are still relevant"*
>
> **National Director of Health Intelligence, Ministry of Public Health, Ecuador**

> *"The themes apply in Nigeria, especially the safety of COVID-19 vaccinations in pregnancy"*
>
> **Research Officer, University, Nigeria**

These results clearly demonstrate that the combined consensus-gathering approaches (survey and workshop) were successful in identifying accurate and relevant priorities for pharmacovigilance in LRSs during the period of the COVID-19 pandemic in question. These findings also provide further justification to the method of priority identification adopted in the survey, specifically the assessment of individual knowledge gaps (see **28.5**). Whilst, following the survey, it was argued that that knowledge gaps could be equated to priorities, in the workshop, the items identified in the survey were explicitly agreed to be pharmacovigilance priorities in LRSs during the COVID-19 pandemic by the participants.

32.5 Polling Methods

As noted, the workshop software polling function did not provide the ability to limit the number of in-workshop poll responses. This presented a challenge, given the aim for poll participants to select precisely three response options (see **19.1**).

The software limitations were known prior to the workshop (by virtue of poll function testing, see **19.1**). Nevertheless, it was decided to proceed with an in-workshop poll to ensure that participants

completed the poll whilst the workshop discussions were 'fresh in their minds', and to increase response rates (in comparison to a post-workshop poll distributed via email).

A number of steps were taken in an attempt to ensure that participants provided the correct number of poll responses (n=3). Written polling instructions, stipulating that respondents should provide three (and only three responses), were presented onscreen in the workshop prior to the poll, and were read aloud by a researcher. Similar instructions were also included in the poll questions, which were visible to all participants as they completed the poll. Finally, verbal reminders to only select three responses were repeated at intervals throughout the in-workshop polling period (approx. five minutes) by a researcher.

Despite these measures, 15.9% of in-workshop poll respondents provided an incorrect number of responses (range = 1-9). The average number of responses provided per person was 3.27.

Given that the majority of participants selected the correct number of responses, and that the mean number of responses differed from the target mean by <10% (0.3), all responses were included in the final analysis. It is acknowledged that researchers replicating these methods may wish to apply more conservative standards (eg 5% mean deviation) although this will depend largely on the research context.

Technical difficulties encountered during the workshop poll meant that at least eight attendees were unable to view the poll in-workshop. The precise cause of these technicality difficulties could not be determined, although it is believed that differences in software versions were a contributing factor. Some attendees who were unable to view the poll alerted the researchers in-workshop, and all participants who could not see the poll were then asked to identify themselves. These attendees were then sent a link to the post-workshop poll (see **19.5**) for their completion. The post-workshop polling software (Jisc) allowed response numbers to be predetermined, and so all post-workshop poll participants provided the correct number of responses.

The high percentage of workshop attendees that provided the correct number of poll responses demonstrate that the efforts to communicate poll completion instructions in-workshop were largely successful. Nevertheless, it is acknowledged that the final poll results may be influenced by excessive responses provided by some participants, and the need to conduct a post-workshop poll added a further week to consensus-gathering process. It is recommended that researchers looking to adopt a similar methodology do so following careful testing of the polling functionalities of their intended software, with detailed consideration of the polling or voting system they intend to implement, and with an awareness of the advantages and disadvantages of 'in-session' and 'follow-up' testing.

32.6 Workshop Themes

The workshop discussion period was chaired by the members of the ISoP Africa Chapter EC (2019-2022), and included comments on the survey outcomes, the sharing of participant perspectives and experiences in regards to the priorities identified, and questions directed to other workshop participants and panel members. An overview of the major themes that emerged from the workshop discussion period is shown in **Fig. 39**. These are discussed in greater detail below. Note, all job roles provided for quote attributions are reported as described by participants.

The vast majority of verbal contributions to the workshop discussion were from either the chairs (n=4) or the researchers (n=2). Only four participants contributed verbally to the discussion, with one being cut off mid-comment due to suspected connectivity issues (see **Appendix 12**). Nevertheless, panellist contributions were guided and led by questions and comments received from participants via the chat box or Q&A functions.



Figure 39: Themes relating to pharmacovigilance in LRSs that emerged during the workshop.

Data

A broad interest in pharmacovigilance 'data' emerged as a major theme from the workshop discussions, reiterating similar findings from the survey and survey validation process, and expanding on the high interest in 'data analysis' identified in the workshop poll. However, in contrast to the quantitative workshop results which focussed purely on data analysis, data collection and data generation emerged as primary concerns:

"*Obtaining follow-up information could be a major challenge as instead of 2 follow-ups, only 1 follow-up is conducted currently as a result of the pandemic and busy HCPs may not have the time to respond to so many follow-ups especially in countries with large volumes of AEFI reports*"

Country Safety Lead (Emerging Markets), Pharmaceutical Company, Nigeria

"*We still do have countries where we are expected to report manually or [via] paper-based [systems] and requiring physical submission in some countries, yeah? So those are the areas where I personally have had challenges, and we would require to sort of start having discussions around that area to sort of at least level the playing ground for all LMIC countries, so that if you're seeing online reporting, especially now during the COVID pandemic season, then that should be, I mean it should be a minimum requirement for everyone.*"

Chair #3, ISoP Africa Chapter EC

'*There is an inherent assumption that when we do PV, the information we get from the field reports are of good quality. This is not necessarily always the case. And as we collect poor data, we are unable to make good assessments or even provide the necessary feedback back into the field. I think PV in LMIC setting must consider this seriously - How must we improve data collection and also make it easy?*'

Senior Fellow, University, Philippines

The above comments raise a number of considerations. Firstly, that the overburdening of HCPs ('*busy HCPs may not have the time to respond*') has a direct impact on pharmacovigilance data generation in LRSs, and that this phenomenon has been further exaggerated by the COVID-19 pandemic. This echoes findings from both the literature and the survey validation process (see **8.2** and **Appendix 7**), and adds credence to the suggestion first raised following survey validation that workload influences AE reporting culture amongst HCPs. In addition, this highlights the risk of a reduction in ICSRs during times of increased strain upon healthcare systems such as public health emergencies.

Secondly, the comments provide insight into pharmacovigilance capacity inequities across LMICs ('*We still do have countries where we are expected to report manually or [via] paper-based [systems])* and demonstrate how electronic systems are considered the 'baseline' standard for effective pharmacovigilance reporting systems. This theme is further developed by the suggestion

that pharmacovigilance stakeholders in LRS must '*improve data collection and also make it easy'.* These comments indicate that improving the 'usability' of reporting systems (which, it is implied, will in turn drive data generation), for example, via digitalisation, is a good target for pharmacovigilance capacity development initiatives.

Thirdly, the importance of collecting good-quality data, and the impact of poor-quality data, are highlighted. Ensuring high-quality data is especially important in regions with limited numbers of reports and limited capacity (ie LMICs, barriers to collect follow-up information, for example, have been discussed above). High-quality data is a fundamental tool when making evidenced–based decisions regarding medicines safety, without which, populations are exposed to greater risks of medicines-related harm.

In addition to the broader concerns regarding pharmacovigilance data generation in LMICs, the capacity to conduct active surveillance activities in LMICs emerged as an area of particular interest. Whilst it was acknowledged that active surveillance activities were taking place in some LMICs during the COVID-19 pandemic:

> **"***There are a number of countries in Africa that are currently doing one form of COVID-19 vaccine [active] monitoring or the other. I know in Nigeria, there is cohort event monitoring, Ghana has done cohort event monitoring, Ethiopia has done cohort event monitoring, Kenya - so many countries are currently doing cohort event monitoring, and other forms of active surveillance to collect data*"
>
> **Chair #2, ISoP Africa Chapter EC**

The general consensus amongst workshop participants was that greater support for active surveillance activities was needed:

> *[In regards to whether greater support is needed for active surveillance activities] "Yes, [we] do need for more resources, because those projects are usually quite resource intensive and we are experiencing that in Zimbabwe*"
>
> **Head of Pharmacovigilance and Clinical Trials, NMRA, Zimbabwe**

> **"***I think that the support for active pharmacovigilance safety surveillance studies [in LMICs] is required because this is a process that is quite resource intensive*"
>
> *"[In relation to conducting active surveillance activities] Support is needed. I don't think it's adequate as yet, and as you see the priorities from [the survey findings] it is important both from the patient side, from all stakeholders, the whole post market surveillance [sic], especially [in] low and middle-income countries [it] is an important issue*"
>
> **Chair #1, ISoP Africa Chapter EC**

The above comments suggest that the resource-intensive nature of active surveillance activities is the primary barrier to their conduction in LMICs. Nevertheless, the precise resources that are lacking were not determined during the workshop, and it is recommended that further research is undertaken to investigate these barriers in greater-depth.

In addition to discussing the challenges surrounding pharmacovigilance data in LMICs, an interest in existing pharmacovigilance reporting tools in LMICs was also raised:

> "*Could [the panel] or members in the room comment on their experience with usability and/or availability of tools available (eg the Med Safety App or others you use in your countries), to support/advance work in the reporting and monitoring of adverse events associated with medicines and vaccines used during the pandemic?*"
>
> **Independent Consultant, Pharmacovigilance Consultancy, Germany**

Specific reporting tools identified throughout the discussion included the WEB-RADR Med Safety App (as demonstrated above), national electronic reporting systems, MSH/SIAPS's Pharmacovigilance Monitoring System (PViMS) and UMC's VigiFlow.

Research

Another theme that emerged from the workshop discussion was 'research'. Through questions directed to the workshop panellists, some participants requested further information regarding ongoing COVID-19 pharmacovigilance research activities in LMICs:

> *"Does ISoP have any particular ongoing research on COVID-19 Vaccines in the West Africa region?"*
>
> **Vaccine Security and Logistics Consultant, Human Resource Consultancy, Nigeria**

This interest contrasts with the lower ranking of the item '*Ongoing global COVID-19 PV work and stakeholders*' in the workshop poll (ranking; =9th). This may indicate a greater interest in more localised, regional research activities (eg '*in the West Africa region'*) as opposed to 'global' pharmacovigilance activities. Alternatively, given the overview of African pharmacovigilance activities during the COVID-19 pandemic provided by the workshop Chairs (see **Appendix 12**), it may be that poll participants felt relatively informed of ongoing global activities following the workshop discussion, contributing to the item's lower ranking as a priority.

Other participants sought to emphasise a lack of pharmacovigilance research in their settings during the pandemic:

> *"In Uganda, we have not conducted a pharmacovigilance/safety research during the pandemic [sic]."*
>
> **Biomedical Laboratory Technologist, University, Uganda**

These comments conflict with remarks made by a number of the workshop chairs, who suggested that COVID-19 pharmacovigilance had taken place in several LMICs during the pandemic, including in the country specified above (albeit, not focussed on COVID-19 pharmacovigilance in pregnancy, see above). This is confirmed in the literature. This confusion appears to demonstrate a lack of awareness of local COVID-19 vaccine safety research amongst pharmacovigilance stakeholders in LMICs.

Collaboration

Collaboration was another key theme that emerged during the workshop discussion. This was driven by participant questions and examples provided by workshop chairs:

> "*What structured cooperation/collaboration is in place in Africa to share PV workload and encourage PV learning from experience?*"
>
> **Managing Director, Pharmacovigilance Consultancy, UK**

> "*Kenya was among the first countries that implemented [an electronic AE reporting system in Africa] and through this, there's been sharing of information, and [pharmacovigilance stakeholders from] countries like Tanzania, Rwanda visiting and training with Kenya, capacity building, just to see how this is working, and then they [are] able to implement the same in their countries. We've [also] had [pharmacovigilance stakeholders visit from] Zimbabwe, which also is one of the countries that was able to work with Kenya and implement this*"
>
> **Chair #4, ISoP Africa Chapter EC**

In addition to the sharing of previous and existing examples of pharmacovigilance collaborations in/across LMICs, the value of collaborative approaches to pharmacovigilance capacity building was raised:

> "*Apart from just the support that could be extended towards LMICs, I think, also collaboration is key, because reinventing the wheel becomes more expensive, so for the countries that have done it and for the countries that are looking at doing it, I think these conversations and just leveraging on the already available resources will also go a long way in strengthening the capacity, rather than everybody wanting to go alone to call the shots*"
>
> **Chair #4, ISoP Africa Chapter EC**

The above comment highlights that collaborative approaches are considered beneficial due to their potential to reduce the economic burdens of pharmacovigilance activities, their greater efficiency (via avoidance of the duplication of effort), and their departure from individual exceptionalism ("*everybody wanting to go alone to call the shots*") in the conduct of pharmacovigilance.

Communication

'Communication' was another topic of interest that emerged during the workshop discussion. For comparison, the item '*How to effectively communicate COVID-19 vaccine/medicine safety information*' ranked 5th in the workshop poll. This parallels the emergence of 'Communication' as a theme from the survey qualitative responses (see **28.4**). Comments mainly focussed on incidences of failures of pharmacovigilance communications in LMICs and their impact:

> *'I believe the key issue facing LMIC [sic] is safety communication. There is some lack of hesitance and confidence in communicating safety information, creating an environment of lack of trust between the ministries, regulators and the public has a ripple effect, vaccine hesitance, infodemics becomes unmanageable.*'
>
> **Senior Program Officer, Intergovernmental Organisation, Uganda**

> '*PV information does not reach the users of vaccines and more fear is raised when different vaccines are used for first jab and second or booster [sic]. This needs to be improved through the communication media'*
>
> **Quality Assurance Advisor, Clinical Research Centre, US***

As outlined in the above comments, poor communication of vaccine safety information is associated with the propagation (or perpetuation) of negative emotional responses amongst the intended recipients (mistrust, lack of confidence, hesitance, fear). In turn, this contributes towards negative attitudes towards vaccination, increased vaccine hesitancy, and reduce vaccination coverage. Two specific drivers of poor communication are alluded to; lack of confidence of the communicators (perhaps suggesting a lack of communication training, a lack of expertise regarding the items to be communicated, or lack of personal confidence in the item being communicated) and a failure to disseminate information to all stakeholders.

In addition, participants provided further elucidation as to the precise loci on the pharmacovigilance spectrum (ie between which stakeholders) that represented priorities for communication improvement:

"*The communication between the population and the national authorities need to be improved*"

National Director of Health Intelligence, Ministry of Public Health, Ecuador

"There is a lot of hesitancy in reporting, where the healthcare workers feel that they do not get any feedback"

Pharmacovigilance Specialist, Hospital, Kenya

In both of the above incidences, whether in reference to the general public ("*the population*", also see above, "*the users of vaccines*") or to HCPs, the comments demonstrate that major bottlenecks to pharmacovigilance in LMICs lie in the failure of regulatory authorities and policy makers to communicate safety information effectively to 'grassroots' stakeholders, namely HCPs working at a clinical level (the 'patient interface') and patients.

Support and Information

Many of the comments shared above reference the need for greater support, or include explicit calls for support, for pharmacovigilance activities in LMICs during the pandemic. In addition to the above, some participants highlighted or suggested further areas in which support was needed for, or methods by which further support could be provided:

"*Maybe even registries can be considered or harmonized surveillance systems that are regional, that can quickly answer this [in respect to resource limitations], because of the resource requirements needed [sic]*"

Chair #1, ISoP Africa Chapter EC

"We need support in keeping up with new information as healthcare workers, contributing [to] real-world data. If more is reported and shared, case studies, it will help in building knowledge, and those who are working at health facilities can be able to provide better patient information. There are fears amongst those with co-morbidities, pregnancies, and we need to create complete confidence to assure our patients"

Pharmacovigilance Specialist, Hospital, Kenya

The suggestion for regional systems harmonisation echoes both the calls for greater collaboration, and the need for greater support to conduct more resource intensive pharmacovigilance such as active surveillance, discussed above. Additionally, the need to improve the provision of novel safety information to healthcare workers, to in turn to provide better information to patients, reflect the concerns raised regarding information dissemination to HCPs and patients above.

Whilst there were many references to the need for greater support for pharmacovigilance activities in LMICs during the workshop, the potential sources of such support were not elaborated upon. In reality, it is likely that greater support is sought from a wide range of stakeholders, including via LMIC-LMIC, and LMIC-HIC collaboration. Needs for further support were identified by participants with a range of backgrounds and professions, and so no particular professional group (regulators, the pharmaceutical industry, HCPs etc) can be singled out in bearing a greater responsibility to provide increased support to another. Whilst further investigation may provide greater clarity as to which groups are considered to be key support providers, these findings augment the above calls to strengthen collaboration amongst pharmacovigilance stakeholders in LMICs (see collaboration).

In addition to calls for support, some participants made explicit requests for pharmacovigilance information:

> "*Is there any website or reliable source of emerging (new) information where the safety of the COVID-19 vaccine can be sought be health professionals*?"
>
> **Pharmacist, Regional Health Authority, Kenya**

> "*Please will like some of the tools web site [sic] be outlined for us to know them and used appropriately. Thanks*"
>
> **M&E Focal Person/Pharmacist, Regional Health Authority, Nigeria**

"*Do we have information on the safety of COVID-19 vaccine on nursing mothers, especially on breasting feeding [sic]?*"

Research Officer, University, Nigeria

These requests, and the diversity of their topics, demonstrate both a general lack of pharmacovigilance information, and a lack of awareness of where to find such information, in LRSs. Whilst 'information' was never explicitly defined by any participant, as a workshop theme it is broad, encompassing written guidance and evidence, pharmacovigilance data, and tools and resources.

COVID as an Opportunity

Whilst much of the discussion focussed on to the challenges facing pharmacovigilance in LMICs during the COVID-19 pandemic, and priority areas for improvement, several participants raised that the pandemic presented an opportunity to catalyse the improvement of pharmacovigilance activities in LMICs:

"Do you think these priorities can be extended beyond the pandemic? I can see that they focus on safety mostly which is relevant across board?"

PhD Student, University, UK

"*I think the current pandemic can be a huge opportunity to make healthcare professionals and general public aware of the various ADR reporting tools. This can be of benefit post pandemic as well*."

Lecturer and Researcher, University, Zambia

"COVID-19 has brought a lot of good things, in addition to not-so-good things, but some of the benefits that we can all appreciate is the fact that online communication [has] opened channels, especially between regulators and the rest of the stakeholders, including… participants from the manufacturing companies, as well as many people who support the pharma industry"

Chair #3, ISoP Africa Chapter EC

> "*I think it really presents an opportunity for countries to identify [COVID-19 vaccine safety] data related to pregnancy. Now probably a number of countries have also approved, I don't know how many countries, in Africa have approved the vaccination in children. I think it also presents us an opportunity to collect that kind of data in real life, to see how these vaccines are working, and I think it does remain an area of priority, or it should remain an area of priority, that people can focus on and, hopefully, we can do more studies. We can put additional effort [in] to collect data in those areas that can inform policy decisions related to the vaccines*"
>
> **Chair #2, ISoP Africa Chapter EC**

Specific areas of 'opportunity' included; harnessing the increased awareness of the importance of pharmacovigilance and pharmacovigilance activities amongst HCPs and the general public; maintaining the momentum of increased pharmacovigilance activities, and applying the lessons learnt to pharmacovigilance concerns beyond the pandemic; embracing different methods of working and increased connectivity; making the most of the enormous amounts of safety data generated by global mass immunisation on an unprecedented scale.

Many overlaps can be seen between these opportunities and the themes previously discussed. Contrastingly, these comments present an alternative, more positive dialogue to the discussions of 'challenges' and a focus on areas for improvement, and bring further attention to the successful pharmacovigilance work being conducted in LRSs during the pandemic.

Moreover, the comments highlight a desire to strengthen proactive approaches to pharmacovigilance in LRSs. Not only can new developments, spurred by the COVID-19 pandemic, be leveraged to improve routine pharmacovigilance activities, but the knowledge and strategies that have proved valuable and successful can be used to inform preparations for future public health emergencies. It is likely that this is of particular value to LRSs, regions particularly vulnerable to such events.

Africa

Despite the global focus of the workshop ('*What are the Priorities for Pharmacovigilance in LMICs during the COVID-19 Pandemic*?), and the diverse range of countries represented by workshop attendees, the workshop discussion was heavily focussed towards pharmacovigilance activities in Africa, and more specifically, Sub-Saharan Africa. Countries mentioned explicitly in the discussion included Uganda, Kenya, Zimbabwe, Nigeria and Ghana, and several questions from attendees in HICs were also framed with specific regards to pharmacovigilance in Africa. Nepal was the only non-African LMIC from which verbal contributions were made to the workshop discussion (see **Appendix 12**).

Whilst greater contribution to the workshop from a more diverse range of settings was desired, this outcome is unsurprising. First and foremost, the workshop was chaired by an African pharmacovigilance organisation. It would have been unreasonable to expect the Chairs to offer comments and perspectives on pharmacovigilance activities outside of their own region, and it is only logical that questions directed towards the Chairs sought comment on pharmacovigilance activities in Africa. Second, the majority of workshop participants (56.4%) were based in Africa. Potential explanations for this have been offered above (see **32.1**), however it is also likely that the announcement of the ISoP Africa Chapter EC as workshop chairs during workshop promotion contributed to the high levels of workshop interest in involvement from Africa.

It is possible that a number of other factors influence the higher levels of involvement and contribution from Africa. This could include a greater general interest in pharmacovigilance capacity building initiatives, driven by the particularly low levels of pharmacovigilance capacity described (particularly in Sub-Saharan Africa) in the literature. Alternatively, this interest could be driven by exposure to/involvement in other pharmacovigilance capacity building initiatives, particularly as countries with high levels of project participation (eg Kenya, Nigeria) have

documented involvement in such initiatives. Regardless, these factors have not been assessed in this project, and warrant further investigation before conclusions can be drawn.

In actuality, the impact of the chairing organisation on workshop participation appears to be limited. The survey, a research activity with no immediate involvement of an external collaborator, also saw a very high proportion of African participation (49.7%). Given their first hand and extensive collective experience of pharmacovigilance activities in LMICs, and their closely aligned values with TGHN/GPV, the ISoP Africa Chapter EC (2019-2022) were a clear choice of workshop chair who demonstrated excellent chairing skills and a high level of expertise in the workshop discussions (see **Appendix 12**). Nevertheless, researchers looking to conduct similar global consensus-gathering activities in the future should be aware of the potential of a 'regionally-focussed' panel to introduce regional biases to the research, and may wish to consider ensuring wide geographic diversity amongst their panellists. In any event, such diversity should not come at the cost of expertise.

33 Conclusion

The workshop provided an effective method of determining a clear consensus regarding the immediate priorities for pharmacovigilance in LMICs during the COVID-19 pandemic, where education, training and guidance were needed. Specific priorities for further investigation included the safety of COVID-19 vaccination in Pregnancy, the safety of COVID-19 vaccination in children and adolescents, and the analysis of COVID-19 vaccine safety data.

As with the survey, the GPV membership was demonstrated to represent a diverse pool of global pharmacovigilance stakeholders. Following the identification of these priorities, and given the enormous range of skills and expertise within the community, GPV members are well placed to come together and seek solutions to address these concerns.

Part IV: Implementation

VII Working Groups

Following completion of the consensus building activities and the identification of priority areas of focus for improvement within pharmacovigilance in LRSs, it was decided to establish working groups to address the highest priorities identified. A comprehensive overview of the working group methodology (see **20**) has been provided previously. The component stages of the research cycle were met as follows:

- **Plan:** Working group strategy developed CoP members invited to register their interest in working groups (see **20.1, 20.2** and **Appendix 15**).
- **Act:** Working groups formed, initial group meetings held, online space developed for working groups, initial progress made in resource development (see **20.3, 20.4** and below).

Due to available timescales, the working group action research cycle was not complete at the time of writing. Hence, the 'observe' and 'reflect' components had not yet been undertaken. For a visual representation of the validation methods applied to the action research cycle, see **Fig. 40**.

34 Working Group Objectives

- To establish collaborative working groups focussed on the priorities for pharmacovigilance in LRSs identified in the previous consensus-building activities (survey and workshop).
- To facilitate further in-depth discussion on the priorities identified, expand the topics, and elucidate the challenges and bottleneck within those themes.
- To incentivize discussion on potential solutions to these challenges.
- To support the development of resources and interventions to address these challenges.
- To assess the impact of these resources and interventions when possible.

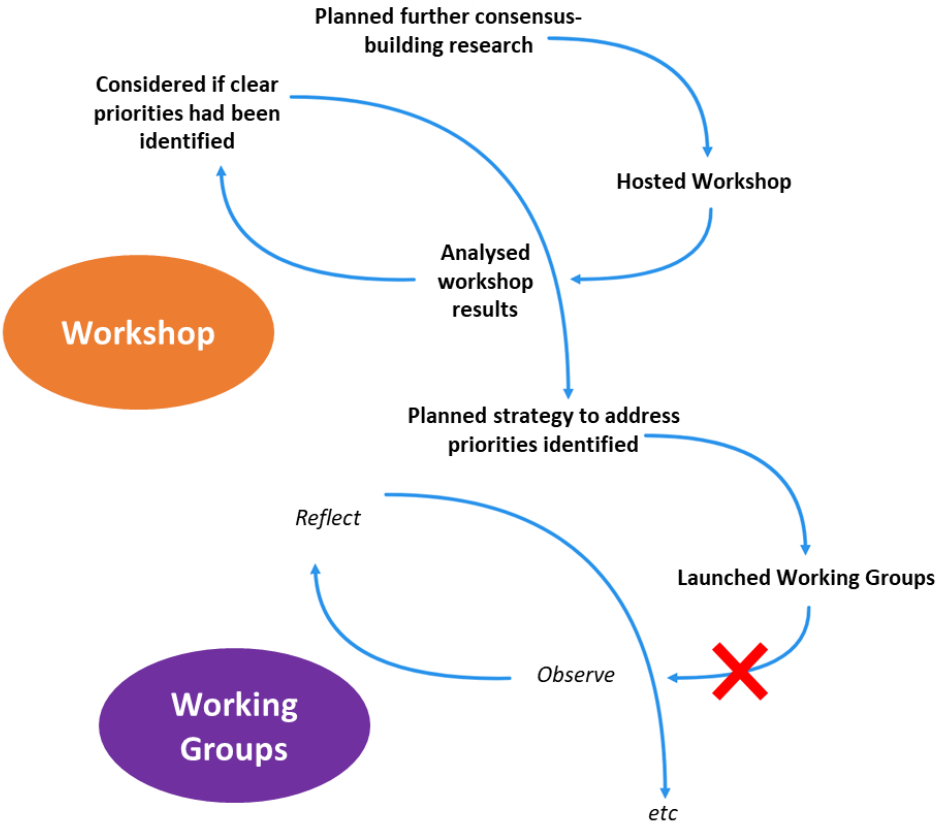


Figure 40: Working Group methodology within the action research cycle. Having been informed by the outcomes of both the validation, the survey (not shown here) and the workshop, the iterative process continued until the cessation of this research. The CoP remains well placed to continue the research cycle (see **44**). Adapted from **Fig. 10**.

35 Results

3 working groups were established in April 2022 to address the three-highest pharmacovigilance priorities or LMICs identified during the workshop, namely:

- The safety of COVID-19 vaccination in pregnancy
- The safety of COVID-19 vaccination in children/adolescents
- Analysis of COVID-19 vaccine safety data

Following discussion in initial group meetings, thematic overlaps were identified between the areas of interest of the 'safety of COVID-19 vaccination in pregnancy' and 'safety of COVID-19 vaccination in children/adolescents'. It was therefore decided by the membership of both groups to merge the

respective activities and form a single group focussing on 'the safety of COVID-19 vaccination in children and pregnancy' in May 2022. Since May 2022, the below working groups have therefore been operating:

- The Safety of COVID-19 Vaccination in Children and Pregnancy in LMICs Working Group (hereafter 'Children and Pregnancy Group/Working Group').
- Analysis of COVID-19 Vaccine Safety Data in LMICs Working Group (hereafter 'Data Analysis Working Group').

35.1 Quantitative Results

Working group registration was open for a 21 week period between March and August 2022. 367 individuals registered as a member of at least one of the working groups (see **Fig. 41**). Of this 367, 49.7% (n=169) expressed an interest in a coordinating role within at least one working group.

Working Groups Membership

As of August 2022, the Data Analysis Working Group had 295 members, and the Children and Pregnancy Working Group had 280 members. Of the collective working group membership (n=367), 56.7% (n=208) were members of both working groups. Therefore, of the Data Analysis Working Group, 70.5% of participants were also a member of the Children and Pregnancy Group/Working Group, and of the Children and Pregnancy Group/Working Group, 74.3% of participants were also a member of the Data Analysis Working Group.

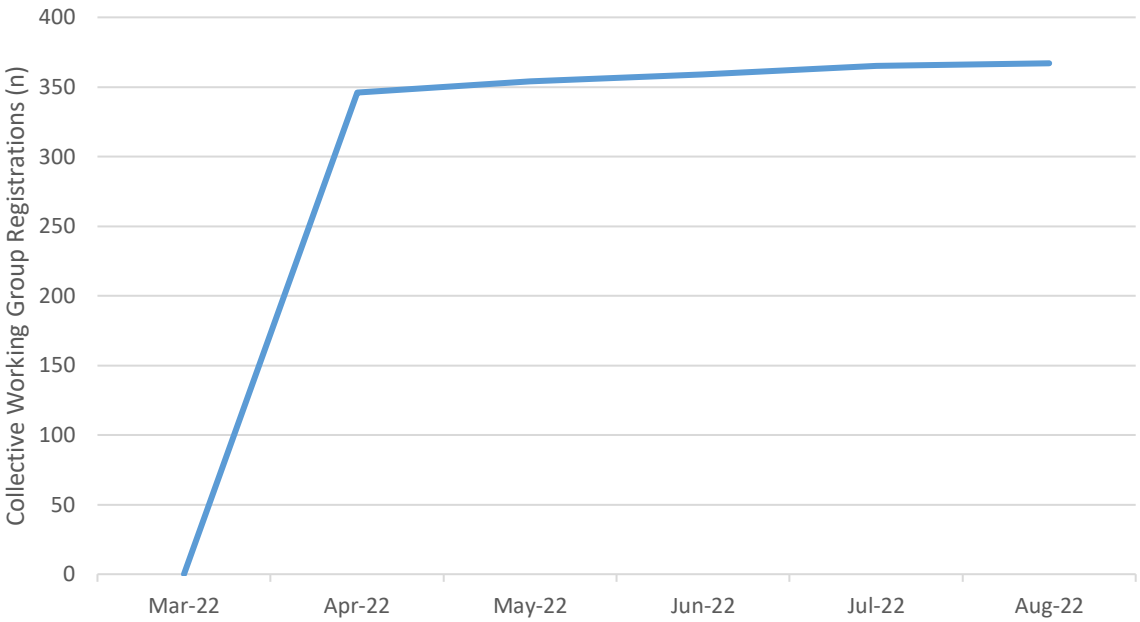


Figure 41: Collective membership registrations of both working groups, Mar-Aug 2022. Registrations were opened on 16/03/2022, and hence the data above reflects total registrations on the 16th day of each subsequent month (16/XX/22). Registrations were closed in Aug 2022.

Demographics: Children and Pregnancy Group

As of August 2022, 71 countries (**Fig. 42.A**) were represented by the Children and Pregnancy Group members (n=280), including 50 LMICs (70.4%) and 21 HICs (29.6%). 84.6% (n=237) of group members were based in LMICs (HICs; 15.4%, n=43). The countries most represented were India (17.9%), Kenya (9.6%), Nigeria (9.3%), Ghana (5.4%) and Uganda (3.9%).

'Pharmacist' was the most common job role held by Children and Pregnancy Group members (35.7%), followed by 'Academic/Researcher' (35.0%) and 'Doctor' (16.8%). 47.5% (n=133) of members indicated that they held more than one job role. The most represented institutions amongst Children and Pregnancy Group members were 'University/College' (28.2%), 'Hospital (Public)' (25.0%), and 'Non-Governmental Organisation (NGO)' (13.9%). See **Fig. 43** for a detailed overview of group member roles and institutions.

55.4% of group members had been involved in pharmacovigilance for five years or less ('less than 1 year', 25.4%; '1-5 years', 30.0%). 19.6% members indicated no previous involvement in

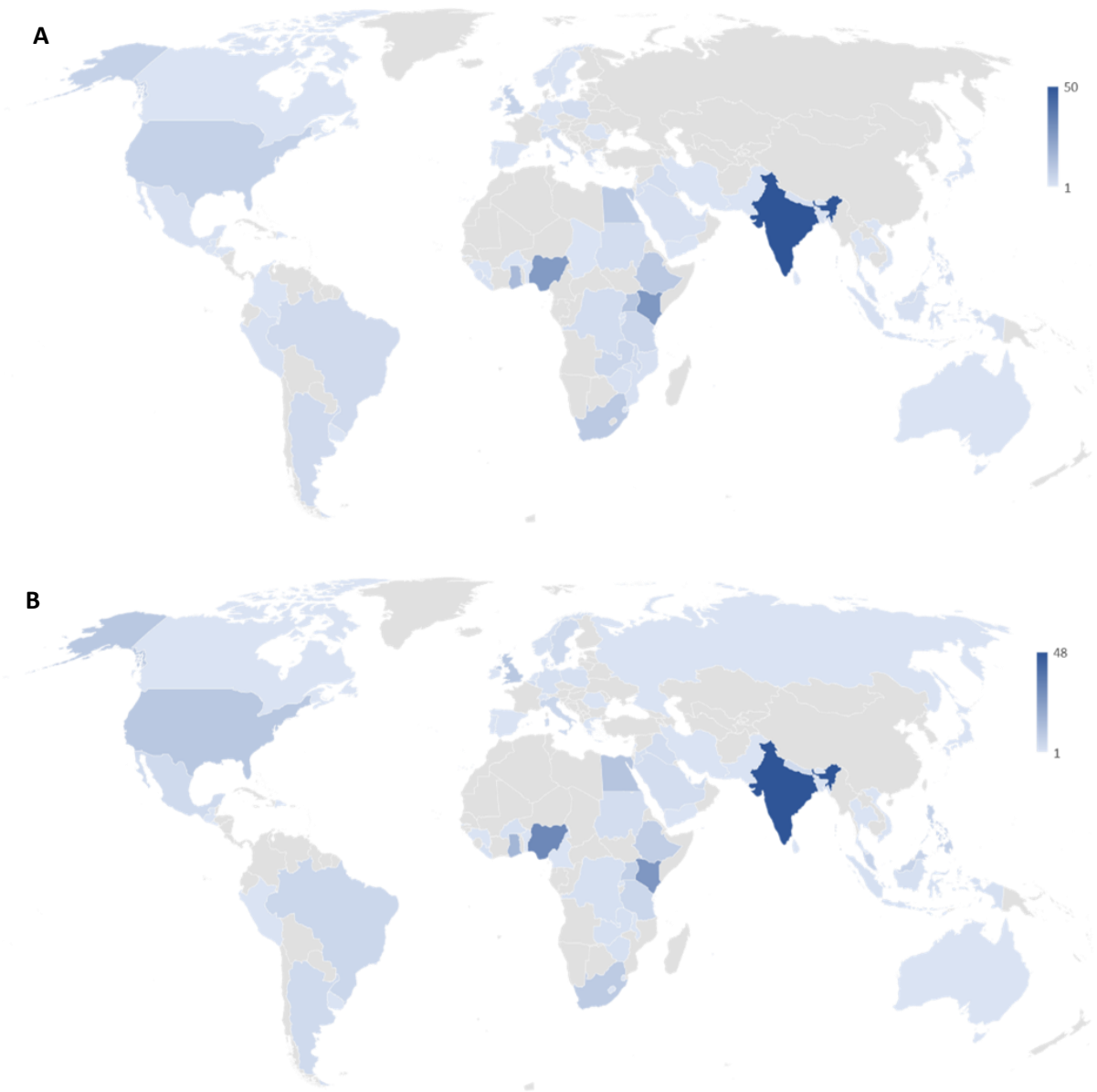


Figure 42: Countries represented by (A) Children and Pregnancy Working Group members (n=280) and (B) Data Analysis Working Group members (n=295), displayed as total members (n). Not visible at this scale are (A) The Gambia (1 member), Mauritius (1 member) and (B) The Gambia (2 members), Mauritius (1 member).

pharmacovigilance at all. 8.6% of Children and Pregnancy Group members had greater than 10 years involvement in pharmacovigilance.

Demographics: Data Analysis Group

As of August 2022, 70 countries (**Fig. 42.B**) were represented by the Data Analysis Group members (n=295), including 47 LMICs (67.1%) and 32 HICs (32.8%). 80.0% (n=236) of group members were

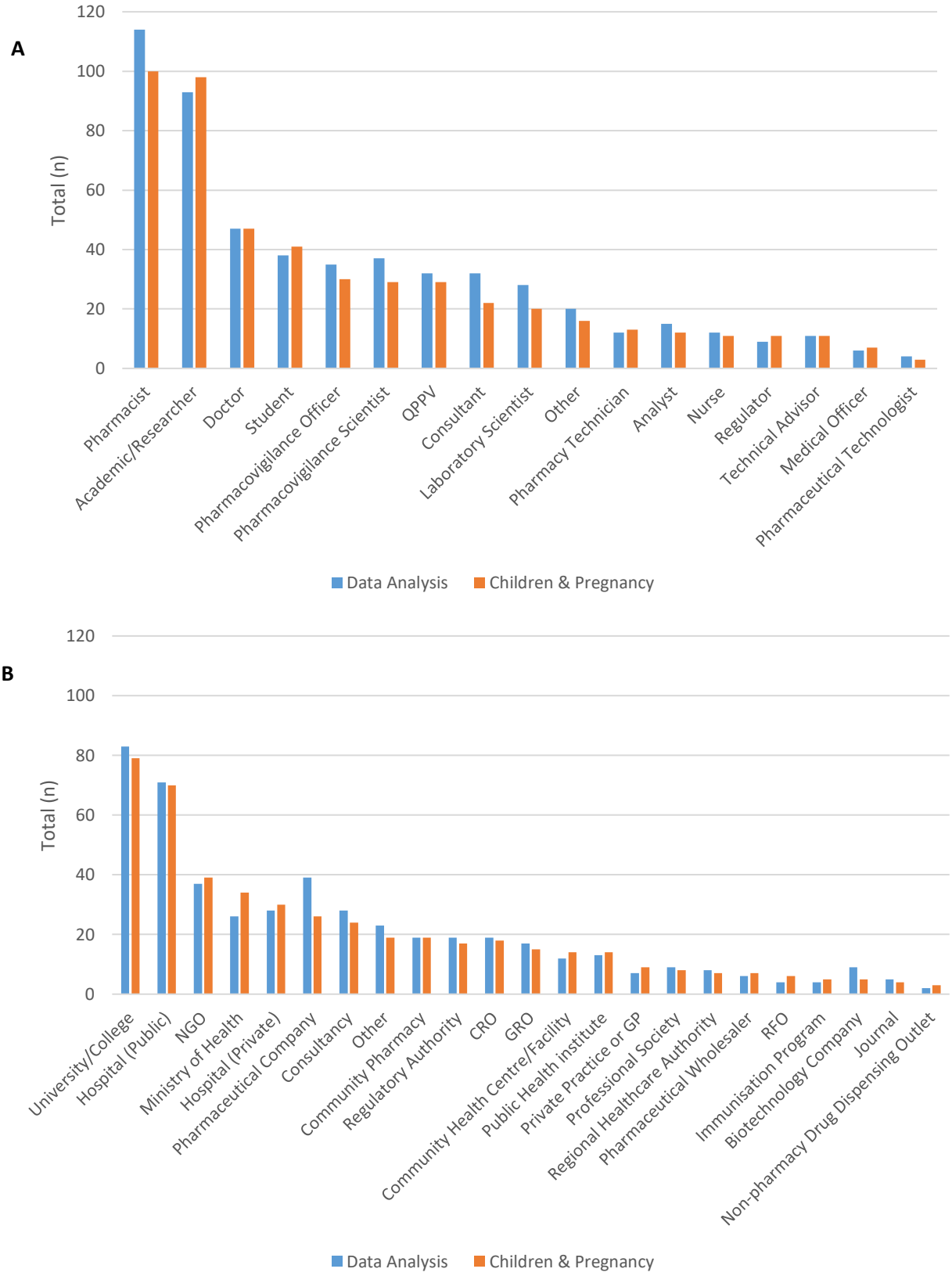


Figure 43: Job roles (A) and institutions (B) of working group members. Note that in the registration form, 'Pharmacy Technician' and 'Pharmaceutical Technologist' (A) were listed as 'Pharmaceutical Technologist/Pharmacy Technician (Clinical)' and 'Pharmaceutical Technologist (Pharmaceutical Industry)' respectively, after it was identified that the term 'Pharmaceutical Technologist' was applied to different roles in different countries and settings.

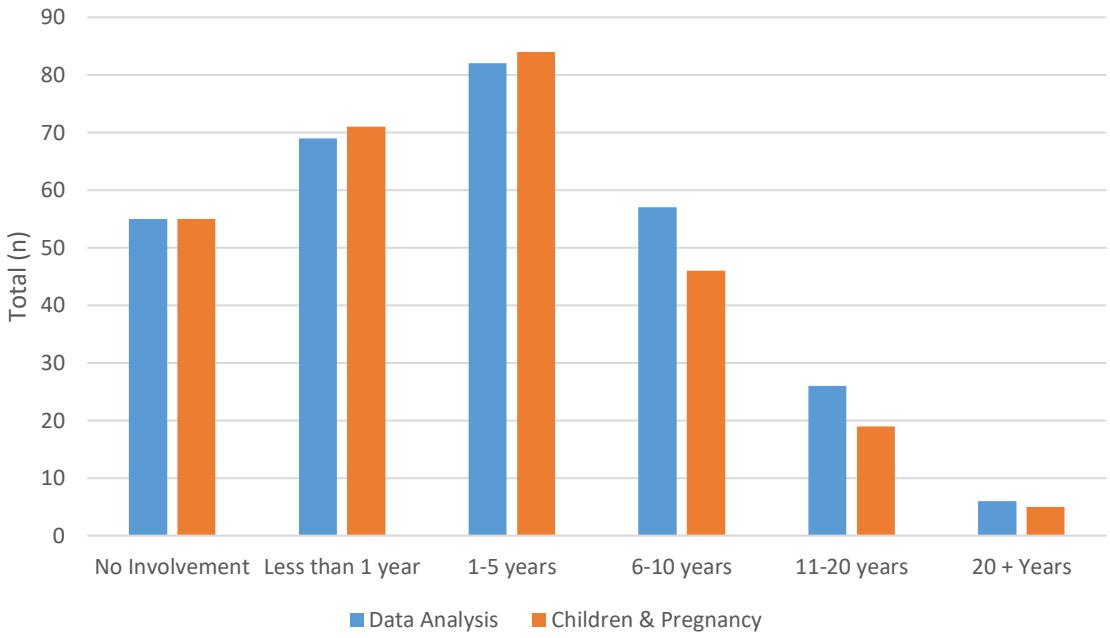


Figure 44: Pharmacovigilance experience of working group members.

based in LMICs (HICs; 20.0%, n=59). The countries most represented were India (16.3%), Nigeria (10.5%), Kenya (8.8%), Ghana (5.4%) and Egypt (3.7%).

'Pharmacist' was the most common job role held by Data Analysis Group members (20.9%), followed by 'Academic/Researcher' (17.1%) and 'Doctor' (8.6%). 49.1% (n=145) of members indicated that they held more than one job role. The most represented institutions amongst Data Analysis Group members were 'University/College' (17.0%), 'Hospital (Public)' (14.5%), and 'Pharmaceutical Company' (8.0%). See **Fig. 43** for a detailed overview of group member roles and institutions.

51.2% of group members had been involved in pharmacovigilance for five years or less ('less than 1 year', 23.4%; '1-5 years', 27.8%). 18.6% members indicated no previous involvement in pharmacovigilance at all. 10.8% of Data Analysis Group members had greater than 10 years involvement in pharmacovigilance (see **Fig. 44**).

Meeting Attendance

5 virtual meetings were held for each working group between April-August 2022. For the Children and Pregnancy Working Group, two meetings of the pre-existing 'safety of COVID-19 vaccination in pregnancy' and 'safety of COVID-19 vaccination in children/adolescents' groups were held before their merger in May/June 2022. Three subsequent meetings of the Children and Pregnancy Working Group were held between June-August 2022.

Working group meeting attendance numbers are outlined in **Fig. 45**.

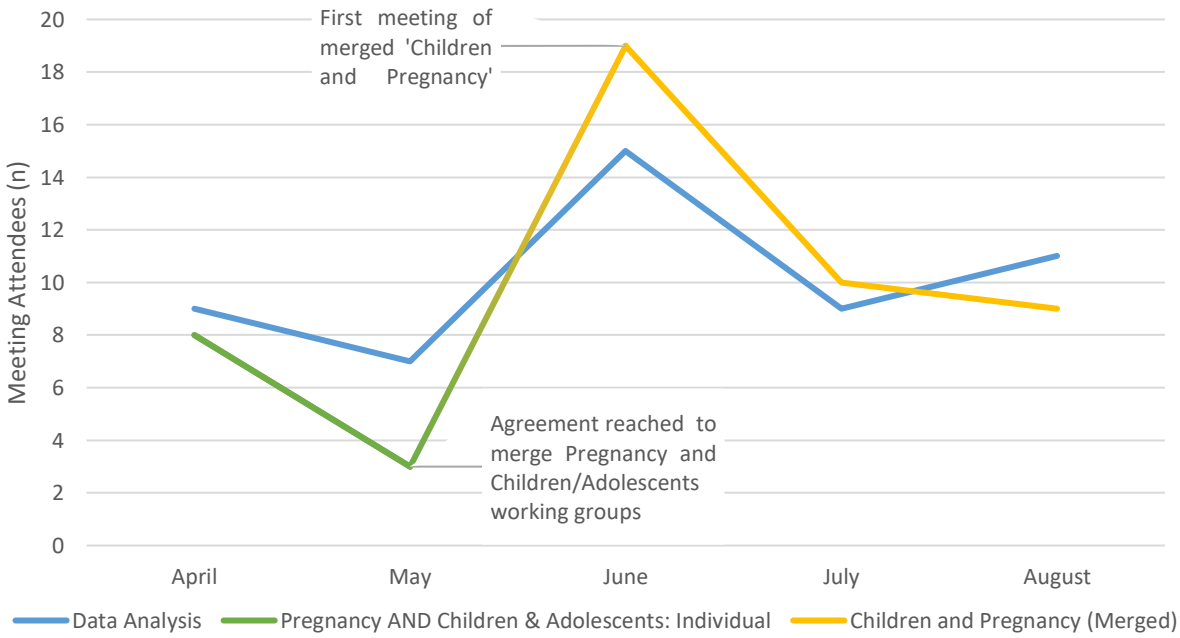


Figure 45: Working group attendance Apr-Aug 2022. Data reflects attendees who were present for a minimum of 50% of the allotted meeting time. The decision to merge the individual 'safety of COVID-19 vaccination in pregnancy' and 'safety of COVID-19 vaccination in children/adolescents' groups was made by group members in their respective May meetings, and the first meeting of the merged Children and Pregnancy Working Group was held in June. Attendance for the Apr (n=8) and May (n=3) 'safety of COVID-19 vaccination in pregnancy' and 'safety of COVID-19 vaccination in children/adolescents' groups was equal for both groups, demonstrated by the single, shared line above. The August Data Analysis Group meeting was postponed due to scheduling conflicts, and was held in Sep 2022. This project's researchers and TGHN digital support team members have not been included in the attendance totals. At least one project researcher was present at all meetings.

35.2 Qualitative Results

Working group discussions were reviewed and summarised to be shared with group members and guide group activities. Summaries of key themes from meeting discussions are presented below.

Children and Pregnancy Working Group Discussions

A lack of awareness regarding the safety of COVID-19 vaccination in children and pregnancy was noted amongst the general public and healthcare professionals in LRSs. It was noted that this can contribute to a lack of public trust in healthcare systems and HCPs. Improving communication of information regarding COVID-19 vaccination safety in children and in pregnancy was identified as an essential strategy to improve awareness and build public trust in this area.

In addition, it was raised that variation in national paediatric COVID-19 vaccination policies may lead to uncertainty, further reducing public trust in healthcare systems and contributing to vaccine hesitancy. It was suggested that greater clarity on the variation in international approaches to paediatric COVID-19 vaccination would be valuable for the general public and professional pharmacovigilance stakeholders.

To address these challenges, the working group planned to develop a serious of short, training and informational open-access videos focussing on 'the safety of COVID-19 vaccination in children and pregnancy in LMICs', with a sub-theme of communication guiding each video topic. In addition, the group planned to create an online resource to map national COVID-19 paediatric immunisation policies. It was acknowledged that the group intended to publish the findings from these activities in an open-access, peer-reviewed journal.

Data Analysis Working Group Discussions

A lack of access to real-time safety data was identified as a key barrier to the analysis of COVID-19 safety data in LRSs. The causes of this lack of accessibility were various and dependent upon setting, but a lack of data sharing between stakeholders, inexistence of publicly-accessible pharmacovigilance databases, and a general paucity of data.

In addition to the concerns regarding data access, it was raised that all pharmacovigilance activities should strive to sensitize HCPs and the general public to the importance of AE reporting and reporting processes; driving data generation remained a prominent theme.

To address these challenges, the working group planned to conduct a multinational research project to promote the accumulation of/access to safety data in LRSs, aiming to conduct a descriptive analysis of COVID-19 ICSRs received by national/regional PV data collectors (eg National PV Centres, Regulatory Authorities, Immunisation Programmes, etc).

35.3 Outcomes to Date

Working Group outcomes as of Sep 2022 are summarised below.

Experience Sharing

In the Children and Pregnancy Group, experiences of COVID-19 vaccination pharmacovigilance and communication were been shared by colleagues in Zambia (*Public Health Researcher, Ministry of Health/NGO*), India (*Academic/Researcher, University/College*), and Burkina Faso (*Academic/Researcher, Government Research Organisation*).

1 meeting of the Data Analysis Working Group (May 2022) was chaired by a group member based in an LMIC (*Pharmacist, Pharmacovigilance Scientist, and Academic/Researcher, Uganda*). In addition guidance on group activities was provided in group meetings by an experienced

pharmacovigilance professional based in an HIC (*Sweden, 11-20 years involvement in pharmacovigilance*).

Both groups engaged in the sharing and dissemination of resources with other working group members via group communications channels (see below).

Website

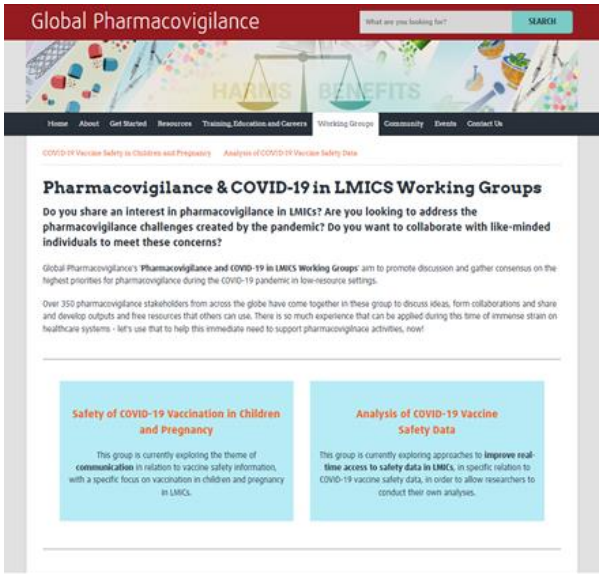
A dedicated space to share the outputs and activities of both working groups was developed on GPV (see **Fig. 46**). This included webpages dedicated to; providing a background to and overview of each working group; the sharing of meeting minutes; an outline of group membership, including demographic information; an overview of each group's current work; the sharing of relevant open access resources relevant to group activities.

Development also began upon an online resource to map national paediatric COVID-19 vaccination policies. This aimed to allow group members to submit information regarding the vaccines used for paediatric COVID-19 vaccination, the age ranges of children being vaccinated, the dosing regimens adopted for paediatric vaccination and provide links to relevant national guidelines relating to their country and/or region. In turn, it was envisaged that this would allow the comparison of varying approaches to paediatric COVID-19 vaccination around the globe.

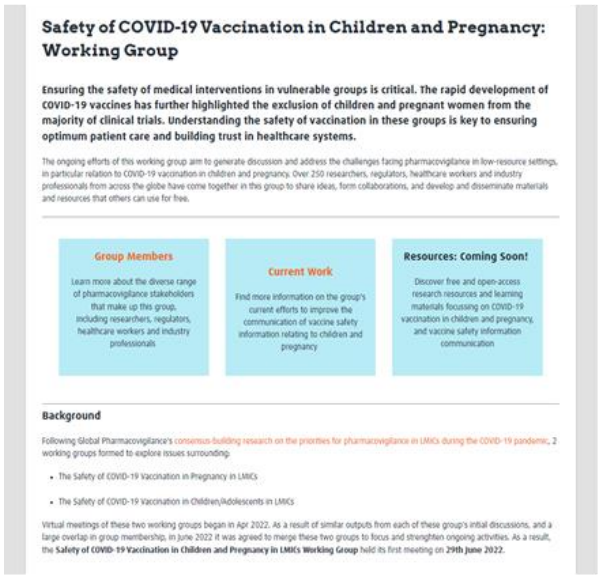
Research Activities

The Children and Pregnancy Group aim to conduct pre- and post-webinar series surveys to assess the impact of the intervention on participant's knowledge regarding the communication of information regarding COVID-19 vaccination in children and pregnancy in LRSs, and to gather feedback on the webinar series.

A



B



C



Figure 46: Screenshots from the working group webpages on GPV, Aug 2022.

(a) Working groups 'home page' page providing a background and overview of both working groups.

(b) A section of the Children and Pregnancy Working Group main page, featuring a group-specific overview and background, and with prominent links to 'Group Member', 'Current' Work' and 'Resources' (in development at time of screenshot) page.

(c) A section of the Data Analysis Working Group 'Group Members' page, showing group demographic information (countries and job role).

The Data Analysis Group planned to conduct a research project to promote the accumulation of/access to safety data, focusing on COVID-19 AESI reports in LMICs (see above). The project also aimed to assess the accessibility of pharmacovigilance data to pharmacovigilance stakeholders in LMICs. Two shared working documents (Google Docs) were created to facilitate group-wide contribution to a research proposal and supportive documents. The group also submitted an abstract regarding its project plans to an international global health research conference, which was accepted as a poster presentation, to be presented in Nov 2022.

36 Outcomes to Date

36.1 Membership

The membership of both working groups grew rapidly in the month following the groups' establishment before plateauing. This was to be expected, given that active promotion of working group registration was only conducted immediately prior to group formation and in the following two weeks. Following the success of the initial recruitment period, reflected in the high numbers of registrations, no further promotion was deemed necessary. The group registration form remained open until it was eventually closed in Aug 2022 following consideration of the low uptake of new members. Nevertheless, interested registrants were still able to join the working groups via

direct contact with the researchers. Approximately 5%[*] of the overall GPV membership registered as a member of a working group. This provided the first plausible outline of the 'mobilisable', potentially active proportion of the total GPV membership. When considered retrospectively, these results provide a much better outlook of the survey response rate (see **28.1**). If for example, a generous active membership of 400 users had been assumed (working group registrations = 367), then the survey response rate would have been 38.8% (n=155), well above the minimum target of 5%.

A considerable proportion of all working group registrants (49.7%) expressed an interest in a 'coordinating role' within at least one of the working groups, demonstrating a high-level of interest in both active involvement and/or a leadership role within pharmacovigilance capacity-building initiatives amongst the GPV membership. In actuality, a much smaller proportion of group members adopted an active role. The median number of attendees across all meetings[†] for both

[*] Using an approximate total membership of 7500, see

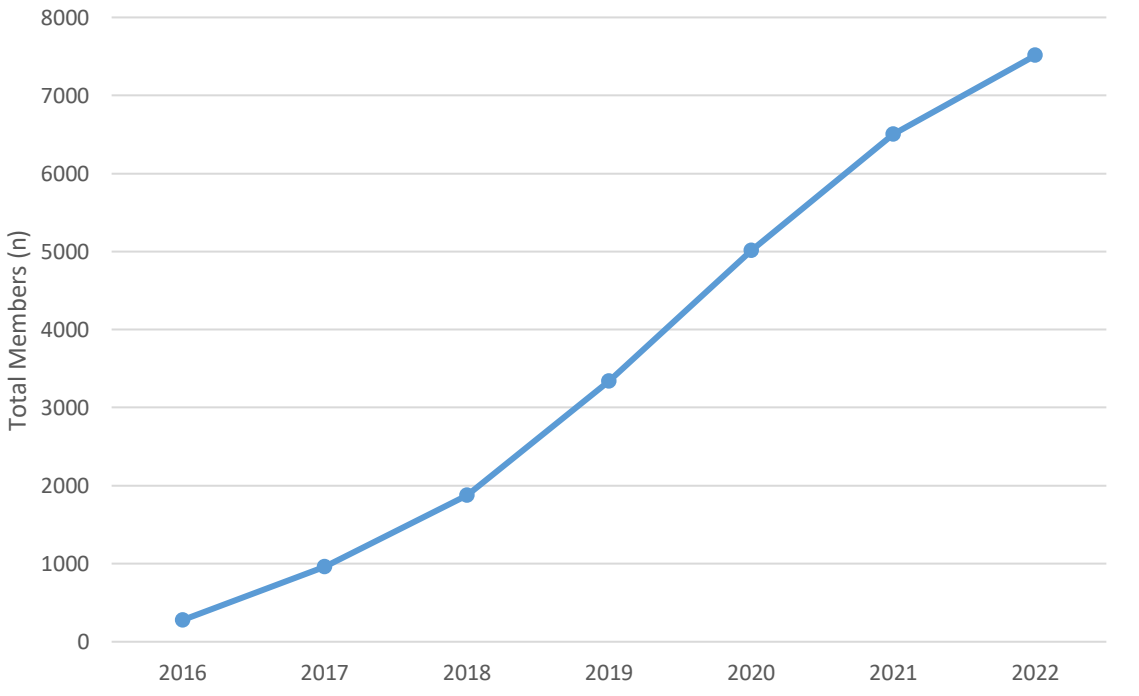


Figure 47.

[†] Group meetings were described as 'coordinator group meetings' in communications.

working groups was nine (see **Fig. 45**), 2.5% of the total working group registrants, and 5.3% of the total that had expressed an interest in a coordinating role.

Whilst these final figures seem small, from a practical consideration they are beneficial; a coordinating group of 150+ members would be inefficient and challenging to manage. The failure of the high-level of interest in group coordination to manifest into active involvement is likely due to a combination of factors; the relative ease of 'expressing interest' in comparison to regular active commitment to group activities, uncertainties regarding the necessary requirements of the role, and changing personal responsibilities and commitments. Regardless of these considerations, the level of active engagement in group meetings, and enthusiasm of the group members was considered to be excellent, and each group was led by a passionate and motivated group of individuals.

The high degree of shared interest between the working groups, despite the seemingly disparate topics of interest, reinforced the findings of the earlier research activities; there are many diverse, distinct elements of pharmacovigilance in LRSs in urgent need of improvement during the COVID-19 pandemic, and there is a great interest in collaborating to addressing these challenges. The high level of membership overlap could have led to a reduction in the diversity of the leadership of both groups (ie both groups could have been led by the same people) however, this was not found to be the case, and both groups were led by largely separate groups of individuals.

36.2 **Demographics**

As encountered with the previous research activities, a diverse range of settings and professions were represented amongst the workshop group members.

The majority of participants in both groups were based in LMICs (Children and Pregnancy Group, 84.6%; Data Analysis Group; 80.0%). Similar overlaps were also seen amongst the countries most

represented in both groups (see **36.2** and **39**). These similarities are unsurprising, given the high level of overlap between the memberships of both groups (see **36.1**). Although minimal, greater interest in the Data Analysis Group was noted from HICs (particularly in Europe and America). It is assumed that the greater presence of pharmaceutical companies, and specialist pharmacovigilance organisations (both with a strong interest in pharmacovigilance data analysis) in these regions contributed to this finding.

The majority of working group members were relatively inexperienced (ranging from no previous involvement in pharmacovigilance, to five years' experience, see **Fig. 44**). This matches findings from the survey, and similar conclusions can be drawn (see **28.2**). Experience levels across both groups were very similar, although the Data Analysis group had a higher proportion of participants with medium (6-10 years) and high (>10 years) levels of experience. Despite these lower levels of communal experience, pharmacovigilance stakeholders of all experience levels were represented.

The job roles and institutions represented by working group members were also were also similar across both groups (see **Fig. 43**). Noticeable differences in institution representation include the higher representation of pharmaceutical and biotechnology companies in the data analysis group. This is unsurprising, given the high relevance of data analysis to pharmacovigilance stakeholders working in in these sectors. This is also reflected in the higher number of Pharmacovigilance Scientists, Pharmacovigilance Officers and QPPVs in the Data Analysis group, roles associated with these industries. Some regulatory institutions were more represented in the Children and Pregnancy Group (eg 'Ministry of Health') although the reasoning behind this is less clear. It is possible that this reflects the need of regulators to make informed policy decisions regarding COVID-19 immunisation in these vulnerable groups.

36.3 Outcomes

Group Themes

The discussions held within the working group meetings parallel the previous findings of this research. In the Children and Pregnancy Group, the emergence of 'communication' as a key topic for focus echoes the findings of both the survey (communication-related item 4th highest ranked survey item) and the workshop (see **27.1** and **31**). Similarly, the emergence of data access as a key theme within the Data Analysis working group echoes comments received from the survey validators, the survey ranking (data access-related theme =11th highest ranked survey item) and the workshop (see **27.1, 31** and **Appendix 9**).

The emergence of 'subthemes' within each groups' overarching topic once more demonstrates the complex and highly interconnect nature of many of the aspects of pharmacovigilance discussed in this research. Moreover, the repeated identification of these themes (COVID-19 vaccine pharmacovigilance in children and pregnancy, communicating COVID-19 vaccine safety information, the analysis of COVID-19 vaccine safety data, access to COVID-19 vaccine safety data) throughout each stage of this research conclusively demonstrates them to be amongst the highest priorities for improvement within pharmacovigilance in LMICs during the COVID-19 pandemic.

Knowledge Exchange

The working groups provided effective, focussed forums for active knowledge exchange amongst pharmacovigilance stakeholders in LRSs. Through the sharing of experiences, group members were able to expand their knowledge of ongoing global pharmacovigilance during the COVID-19 pandemic (one of the highest priorities identified in the survey, see **31**) across a variety of LRSs, and to share the challenges they had faced, the lessons they had learnt, seek/offer advice from/to others facing similar areas of concern. This process was further facilitated by the seamless and

frequent communication afforded between group members by the establishment of informal group communication channels, as requested by group members. In addition, the creation of an online space on the GPV platform dedicated to the sharing of relevant materials and resources allowed members to easily access and share training and education materials relevant to the group's domain

Knowledge Generation

Whether deliberately or not, both groups adopted strategies of knowledge generation to address the specific challenges and barriers that they had identified. In relation to the Children and Pregnancy Group, the plans to develop a webinar series focussed primarily on the facilitation of knowledge sharing (information to be provided from experts in the webinar to the participants). Nevertheless, as demonstrate in the group's aims to measure the impact of this intervention, and to map and evaluate international COVID-19 immunisation policies, the group members clearly intend to collaborate in the generation of novel knowledge as part of their activities. The Data Analysis Working Group's commitment is much more explicit; it is hypothesised that the conduction of research harnessing locally-accessed pharmacovigilance data (and hence, the generation of novel knowledge) will promote the need to improve data accessibility in LRSs.

This focus on knowledge generation, as opposed to purely knowledge exchange, to address the challenges facing pharmacovigilance activities in LRSs during the COVID-19 pandemic, represents a shift in the underlying framework of the knowledge community. This is discussed in greater detail in **Chapter IX**.

VIII GPV Platform

An overview of the growth and activities of the GPV platform during the course of this research is provided below. This includes GPV developments that occurred as a direct result of this research, and that occurred as part of GPV's routine refinement and development. In both incidences, these activities were designed to support the GPV membership, and hence the pharmacovigilance CoP.

37 Results

All data described below is for the period Oct 2018-Sep 2022, unless specified otherwise.

37.1 Membership

Since the project's inception (Oct 2018), GPV's membership grew from 1,691 to 7,512 (as of Sep 5th 2022), a total percentage increase of 444.2% (see **Fig. 47**). Membership increased annually by an average rate of 185.7%.

37.2 Usage

The ten countries with the highest level of GPV usage, and the ten LMICs with the highest level of GPV usage (ranked by total sessions, see **21**), are shown in **Fig. 48**. Of the ten countries with the highest level of GPV usage overall, four were LMICs (India, South Africa, The Philippines and Egypt). Of the ten LMICs with the highest level of GPV usage, five were African (South Africa, Egypt, Ghana, Nigeria, and Kenya), four were Asian (India, The Philippines, China, and Pakistan) and one was South American (Brazil). The overwhelming majority of GPV visits from LMICs originated in India (n= 44,917, South Africa had the next highest number of visits, n=2,591).

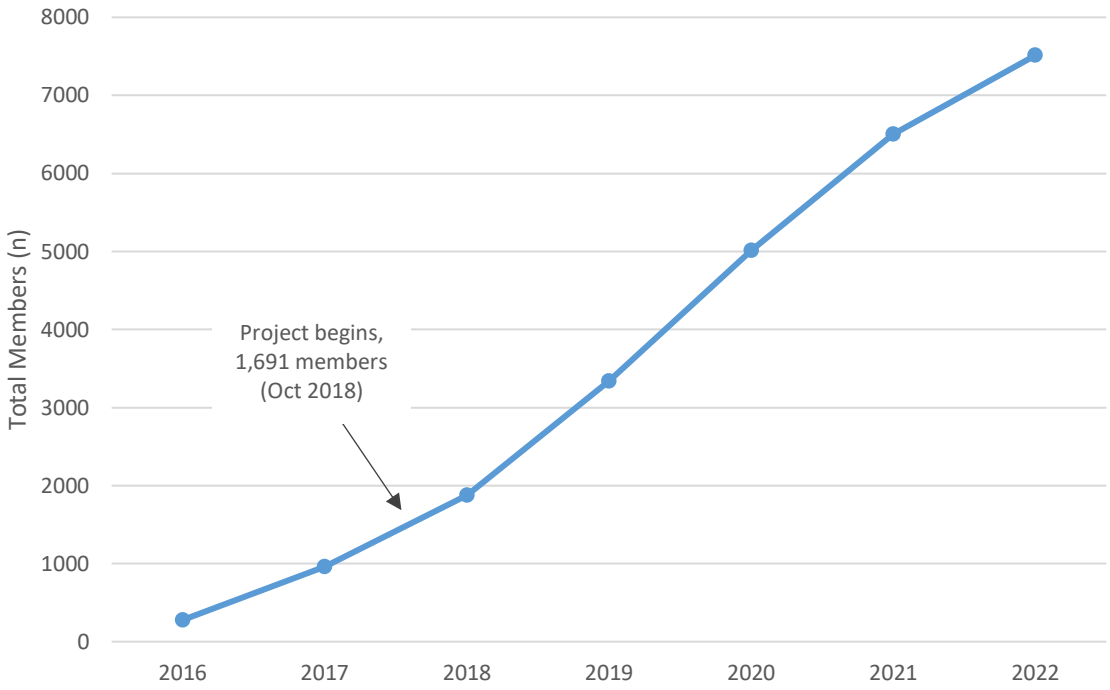


Figure 47: GPV membership over time. Total membership data is taken from the end of each calendar year (31st Dec), excluding 2022 (data taken from total membership at 5th Sep). Note that GPV was launched in June 2016 and hence 2016 data is not reflective of membership growth over an entire calendar year.

37.3 Platform Developments

The GPV platform underwent the following developments during the course of this research, both as a direct result of this thesis, and the routine strategic refinement of the platform the meet its aims and support its members:

Routine Updates

- Restructuring of the 'Resources' repository to improve ease of navigation.
- Development of a webpage dedicated to existing African pharmacovigilance consortia.
- Creation of five additional resource repository pages featuring links to free and open access resources focussed on specific topics within pharmacovigilance, namely:
  - Pharmacovigilance for Herbal and Traditional medicines
  - Pharmacovigilance and COVID-19 (The 6th most-accessed page on GPV over the course of this project)
  - Drug Induced Liver Injury

-

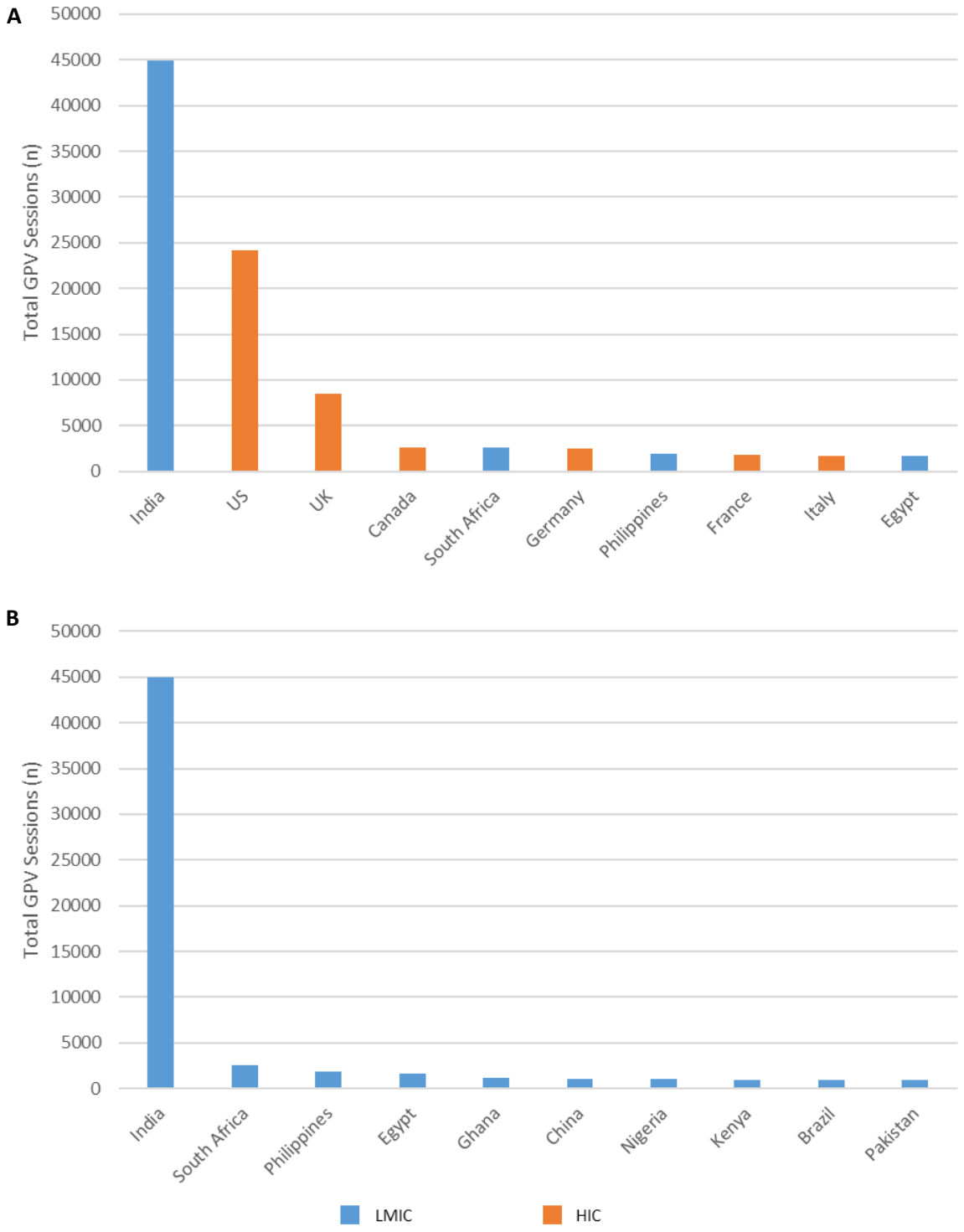


Figure 48: The 10 countries with the highest number of GPV sessions. (A) All countries and (B) LMICs only.

- WHO Global Database for TB Active Drug Safety Monitoring
- Pharmacovigilance and HIV/AIDS

- Restructuring of the 'Videos' library to improve ease of navigation (see **Fig. 49**).
- Expansion and development of 'Featuring Network Participants', a space for GPV members to share their experiences regarding how they came to work in pharmacovigilance, or how they came to conduct pharmacovigilance research, with the aim of providing practical guidance to those seeking a career or post-graduate study in pharmacovigilance (see **Fig. 49**).
- Homepage streamlining and the development of a 'News Archive', to allow the storage and continued access of older news items previously featured on the GPV homepage.

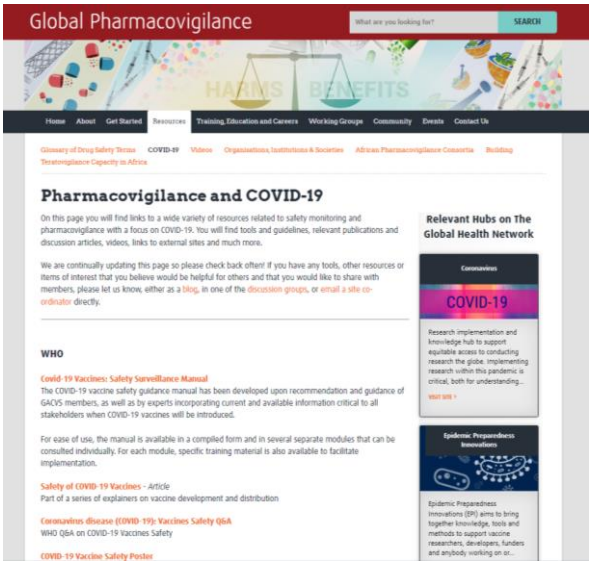
38 Discussion

38.1 Membership Numbers

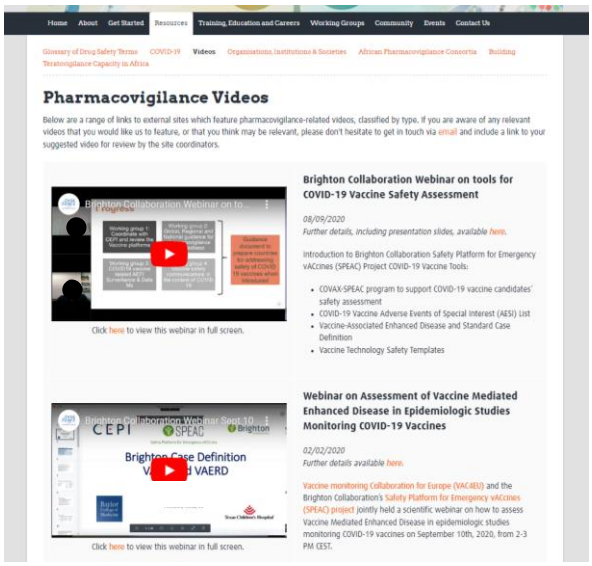
The continued increase in the GPV membership throughout the duration of this research (total increase in membership of 444.2%, see **Fig. 47**) demonstrated an increased, sustained and active interest in both GPV's activities, and the research activities conducted as part of this project, amongst pharmacovigilance stakeholders globally. Given the focus of both GPV and this research on improving pharmacovigilance capacity in LRSs, this suggests a high-level of interest in, and a strong desire to support, pharmacovigilance activities in LRSs amongst the global pharmacovigilance community.

The continued increase in membership numbers throughout the course of the project suggests that inviting involvement in research activities (survey, workshop, working groups etc) was an effective method of driving community involvement. This was further evidenced by the increase in membership numbers following the commencement of research activities (see **Fig. 47**).

A



B



C

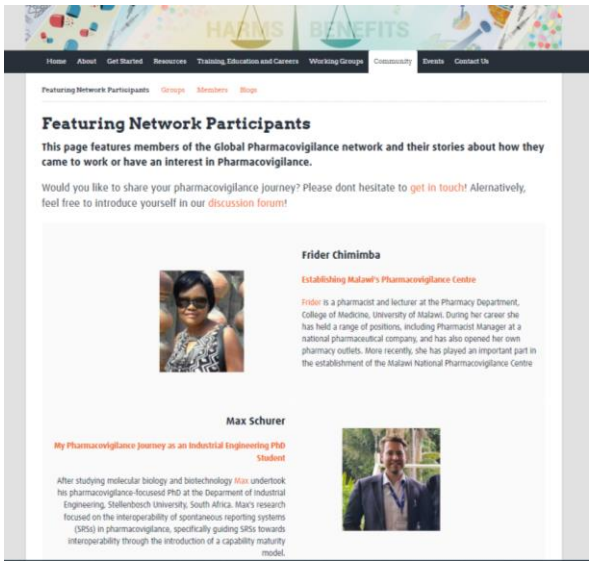


Figure 49: Examples of webpages developed on GPV 2018-2022. Identifiable personal information has been removed where consent was not be received to share it.

A) Pharmacovigilance and COVID-19 resource repository page demonstrating the sharing of relevant open access resources, and links to other relevant TGHN member hubs.

B) A section of the 'Video Library' page following its restructuring to a more interactive and informative arrangement.

C) 'Featuring Network Participants' page, where GPV members are invited to share their experiences regarding how they came to work in pharmacovigilance, or how they came to conducting pharmacovigilance research.

38.2 Demographics

GPV users included stakeholders from a diverse variety of global settings (see **Fig. 48**). This included a high number of users from LRSs. Indeed, the most-represented country amongst the GPV usership was India, an LMIC. This geographic diversity was echoed amongst the participants of the research activities throughout this project (see **39**), and further confirmation of the vast range of skills and knowledge represented within the GPV membership was evidenced in the demographic results of these activities.

Particularly in comparison to other LMICs represented amongst GPV users, the vast majority of platform sessions occurred in India settings (see **Fig. 48**). The motivations behind high-levels of GPV usage in India have not been explored (although discussions of contrasting levels of Indian involvement in research activities have, see **28.2**). Nevertheless, it is logical to assume that India's large population accounts for its much higher usage in comparisons to other LMICs[*].

38.3 Membership Activities

The primary method of membership engagement with GPV was via involvement in this project's research activities. Outside of these activities, the contribution of written articles and reports to the GPV platform was the predominant method of active member engagement. This included five articles submitted for inclusion on the 'Featuring Network Participants' page, see **37.3**), and two articles describing pharmacovigilance methods and research. Each of these was contributed by a GPV members based in, or conducting research in, LMICs.

This adds credibility to the above claim (see **38.1**) that research activities were the most effective method of driving active community engagement. Outside of these activities, initiatives inviting the

[*] Preliminary analysis indicates that these findings are much more balanced when corrected for population: Indian 'GPV Sessions per capita' = 3.25×10^{-5} (assuming a population of 1.38 billion); South African 'GPV Sessions per capita' = 4.37×10^{-5} (assuming a population of 59.31 million).

sharing of personal experience and perspectives were also found to be successful (eg contributions to the '*Featuring Networks Participants*' page, a space for members to share personal stories about how they came to work or have an interest in pharmacovigilance).

These findings suggest two outcomes for consideration: First, that increased interest and engagement in community-based knowledge generation activities is largely dependent on ensuring that community activities have clearly defined aims, scope and intentions (as in the case of the research activities). Second, that engagement can be also driven by inviting participants to share personal thoughts and experiences.

Part V: Discussion

IX General Discussion

39 Context-Relevant Research

In order to ensure that this research had the greatest value and relevance to pharmacovigilance stakeholders in LRSs, it was imperative that research activities were guided by participants based in those regions. In turn, by following the action research spiral (see **11.3**), this ensured that each subsequent research activity was guided by input from stakeholders in LRSs. Participation in this project's research activities was self-selective, and so whilst efforts were made to focus research activities to those working in, or with experience working in pharmacovigilance in LRSs, purely LRS involvement could not be guaranteed in advance.

Efforts to ensure that this research was context-relevant to LRSs were clearly effective, as the vast majority of participants in all research activities were based in LMICs (>75% in all activities, see **Table 14**). Such efforts were largely simple, arguably self-evident activities (ensuring that the LRS scope of the research was conveyed at all stages of research, via inclusion in research activity titles, aims, questionnaire items, documents, communications, targeting individuals in LRSs, etc). Nevertheless, the decision to contextualise the research setting for individual research activities as 'LMICs' in order to ensure contextual clarity for participants, and to reserve the term 'LRS' to contextualise the overall body of work, was deemed important; across all research activities, only one incidence of uncertainty regarding the applicability of the research to a participant's setting was recorded:

> '*Sometimes the wealth distribution is so unbalanced that we can live in an HIC on the public reports but the population is still being treated as an LMIC. Especially the poorer and in need.*'
>
> **Doctor and Academic/Researcher, Panama**[*]
> Survey response to the question 'If you do not work primarily in an LMIC, please briefly describe your interest in pharmacovigilance in LMICs'.

[*] Panama was listed as an HIC by the World Bank in 2021 following a change in classification from Upper-Middle Income Country , and was amongst the countries listed for graduation from the 2021 DAC List of ODA Recipients [30, 31]. However, as of 2022, Panama remains on the DAC List of ODA Recipients as an 'Upper Middle income Country and Territory which is not an LDC'.

Research Activity	Involvement of participants from LMICs (%)	Top 5 countries represented by participants
Survey	85.2%	1. Kenya 2. India 3. Nigeria 4. Uganda 5. Ghana
Workshop Attendance	78.2%*	1. Kenya 2. US* 3. Nigeria 4. India 5. Ghana
Workshop Poll	86.7%	1. Kenya 2. Ghana 3. India 4. Nigeria 5. Uganda
Children and Pregnancy Working Group	84.6%	1. India 2. Kenya 3. Nigeria 4. Ghana 5. Uganda
Data Analysis Working Group	80.0%	1. India 2. Nigeria 3. Kenya 4. Ghana 5. Egypt

Table 14: LMIC involvement and the top five countries represented by participants across all research activities. Note that similar high levels of LMIC participation were also noted in the survey validation process (see **24).** *The US is the only HIC that was one of the top five countries from which there was participation in any of the research activities (Workshop Attendance). Due to the suspected disguising of some attendees' countries resulting from the usage of VPNs, it is likely that the true level of workshop attendance from LMICs was greater than presented here.

Whilst an isolated example, this demonstrates the limitations and inherent assumptions made when adopting umbrella terms like LMIC/HIC in global health research; in this incidence, the failure of a national economic classification ('HIC') to account for regional inequities in wealth distribution. However, such outcomes demonstrate a benefit of the flexible self-selective approach to recruitment in this research; rigid application of the above labels risks the exclusion of valid and relevant perspectives from LRSs in HICs[*].

[*] In van Zyl et al's systematic review (see **I3**) the greatest number of self-reported LRSs identified were in an HIC (US) [32].

With two exceptions (US, Workshop Attendance and Egypt, Data Analysis Working Group), the same five countries were repeatedly represented amongst the highest number of participants at each research activity, namely Kenya, India, Nigeria, Ghana and Uganda (see **Table 14**). Each of these (and additionally, Egypt) is an LMIC. LMIC participation was also in the majority during research development activities (eg survey validation, see **24**).

The US (Workshop Attendance) represents an HIC anomaly (see **Table 14**) amongst these countries. As discussed (see **32.1**), this is most likely to be an inaccuracy brought about by the use of VPNs amongst workshop participants. The 7th highest country for workshop attendance (5th highest if US and UK are discounted due to suspected VPN usage), was Uganda, which is consistent with the other research activities.

There are multiple possible reasons for the consistency in the national representation amongst research participants. Perhaps the most obvious is to link research participation with GPV usage (see **37.2**). Of the six LMICs listed above, two (India and Egypt) are amongst the 10 highest users of GPV, and five (India, Kenya, Nigeria, Ghana and Egypt) are amongst the 10 highest LMIC users of GPV (see **Fig. 48**). It is logical to assume that frequent usage of the GPV platform translates to a greater likelihood of involvement in GPV's research activities, owing to a previous familiarity with the platform, exposure to GPVs communication channels, and a previously demonstrated interested in GPV's activities (inferred via registration as a member).

Nevertheless it cannot be assumed that GPV usage was the only driver for participation in research activities. South Africa, The Philippines, China and Pakistan were each amongst the ten LMICs with the highest level of GPV usage (South Africa was the LMIC with the second highest level of GPV usage after India, see **Fig. 48**) but did not feature amongst the five countries with the highest participation in any of the research activities. Indeed, it is also possible that the reverse is true, and that GPV usage was driven by participation in research activities, particularly in incidences where specific GPV pages have been developed for research activities (eg working groups). In addition,

interpersonal familiarity between the researchers/GPV coordinators and participants or organisations in particular regions (eg ISoP Africa) may have had a beneficial impact on GPV usage in those regions.

It was noted that the five countries consistently represented amongst the countries with the highest level of research participation had varying levels of pharmacovigilance capacity. Of the Sub-Saharan African countries, Nigeria and Uganda were grouped at the highest level of pharmacovigilance capacity '*Group 4 - Countries with performing systems that detect, evaluate and prevent medicine safety issues*' by the Strengthening Pharmaceutical Systems (SPS) programme, whereas Ghana was classified as '*Group 3 – Countries with the capacity to collect and evaluate safety data on the basis of legal and organisational structure*' and Kenya was classified as *'Group 2 – Countries with basic pharmacovigilance structures in place*' [24]. Conflictingly, in Garashi et al's more recent ' *Systematic Review of Pharmacovigilance Systems in Developing Countries Using the WHO Pharmacovigilance Indicators'*, Kenya was found to meet the highest number of WHO pharmacovigilance indicators (n=25), followed by Egypt (n=23), Nigeria (n=18), Uganda (n=11) and India (n=8), (no data presented for Ghana) [80]. Despite these discrepancies in the literature, it is clear that research participation was not limited to LRSs with similar levels of pharmacovigilance capacity (eg only LRSs with more advanced pharmacovigilance systems) and that at all stages, the research outcomes of this project were guided by participants from settings with diverse variations in pharmacovigilance capacity.

It is possible that the countries consistently represented signify regions of greater pharmacovigilance activity. As discussed above, more advanced pharmacovigilance systems have been recognised in some of the countries discussed, and discrepancies in the literature may be a result of increasing levels of pharmacovigilance activity in some regions (eg Kenya, the Sub-Saharan African country with the lowest classification in the SPS classification, 2011, but the country meeting the highest number of WHO pharmacovigilance indicators in 2022) [24, 80]. Stakeholders

in both Kenya and Nigeria have been involved in international pharmacovigilance capacity building initiatives, regulatory organisations in both Kenya and Ghana have been designated RCOREs in pharmacovigilance by the AMRH programme, and the Pharmacovigilance Program of India is a WHO-CC for pharmacovigilance (see **8.2**). However, a comparative assessment of ongoing pharmacovigilance activities in the countries participating in this project, and the relationship between national pharmacovigilance activities and involvement in pharmacovigilance research, is outside the scope of this work and has not been explored here.

In addition, it is acknowledged that higher levels of research participation from particular countries were likely influenced by this project's initial focus on pharmacovigilance in Africa, the study language (English), and time zones, particularly in relation to 'fixed-time' research activities (eg the Workshop and Working Group Meetings). It is also possible that the consistency in the countries represented implied consistent engagement of individual participants in the project's research activities, although individual participant 'project commitment' was not investigated.

Despite the above considerations, it is clear that this research has been guided chiefly by participants from a wide range of LRSs. The diversity of countries and geographic regions represented during each research activity ensured that input and perspectives were gathered from across the entirety of the global pharmacovigilance ecosystem. This geographic diversity, coupled with the high level of LMIC involvement at all stages of this research, supports the conclusion that the findings of this research are relevant and applicable across LRSs globally.

40 Engaging all Stakeholders

To achieve the aims of this research, it was necessary to engage pharmacovigilance stakeholders at all points on the professional spectrum. Balanced representation across all relevant sectors was deemed essential to ensure that challenges were identified in relation to all pharmacovigilance

activities, and to ensure an extensive and resourceful pool of collective community knowledge to support knowledge sharing activities.

As discussed above (see **41**), efforts to recruit a diverse pool of participants were highly successful. In addition to the geographic diversity, a vast range of professions and organisations were represented. Each research activity involved participants from key pharmacovigilance sectors, including healthcare facilities, the pharmaceutical industry, academia, regulatory bodies, consultancies, private research organisations and public health programmes (see **24.1**, **27.1**, **31.1** and **35.1**).

Pharmacists and Academics played a particularly a large role in each stage of the research. The causative factors behind this have not been precisely determined, although medicines safety activities amongst HCPs may logically be considered to primarily be the remit of the pharmacist, the clinical 'medicines expert', and the interest of academics in research activities is predictable. Despite these majorities, the findings represent significant contributions from distinct sectors, and a large number of other roles and organisations were represented.

There was little-to-no patient involvement in this study (although a patient representative did contribute to the workshop discussion, see **Appendix 13**). Although it is possible that participants provided responses during research activities from a personal patient perspective in addition to the professional role that they provided, this was not measured.

As the stakeholder that the science seeks to protect, patients are ultimately the most important stakeholder in pharmacovigilance [173]. Despite this, the lack of patient involvement in this research is unsurprising; It is uncommon for pharmacovigilance systems in LRSs to provide processes for patient reporting, awareness of pharmacovigilance amongst the general public in LRSs is low, and it is assumed that an individual would be unlikely to actively register as a member of a specialist pharmacovigilance platform (GPV) without some level of professional interest in pharmacovigilance. Nevertheless, future efforts to reach consensus on the priorities for

pharmacovigilance (regardless of setting) should continue to seek involvement from a diverse range of stakeholders, including patient participation where possible.

41 Pharmacovigilance in LRSs

The findings of this research clearly echoed the findings in the literature; the challenges facing pharmacovigilance in LRSs are multifaceted and tremendously complex (see **8.2**). This was evidenced by the enormous scope and diversity of relevant themes and topics identified in both the quantitative and qualitative results at all stages of this research. Many of these challenges have been further exacerbated by the COVID-19 pandemic.

This multiplicity presents a challenge in itself. In order to build pharmacovigilance capacity in LRSs, there is a clear need for processes which facilitate the democratic and systematic identification of priority-areas for improvement, in order to ensure the most valuable and effective application of resources (see **42**). Again, this is particularly valuable in times of public health crises, to facilitate the rapid sharing and advancement of knowledge

Despite this heterogeneity of these barriers, the continued emergence of similar items and themes during consensus-gathering activities throughout this research has identified several interconnected but distinguishable key areas for focus and improvement in pharmacovigilance in LRSs during the COVID-19 pandemic.

The first is ensuring the safe use of medicines in vulnerable populations. Several key populations of interest were identified, including children and adolescents, pregnant women, and those with co-morbidities. These populations are of particular relevance to LRSs, given general demographic profiles (younger populations) and the high proportion of the global disease burden (see **32.3**). The greater degree of uncertainty surrounding the use of medicines in these populations, and the sensitivity of the general public to the risks of medicine related harms (especially in children and pregnant women) in these groups is likely to be a significant contributor to higher levels of mistrust

in healthcare systems. Establishing the safety of medical interventions in such populations in LRSs is therefore critical to building public trust, particularly in times of mass drug administration/immunisation and healthcare emergencies.

Secondly, communication of pharmacovigilance information can be improved at all levels of the pharmacovigilance spectrum. 'Communication' was noted to be a driver of two additional elements, 'Awareness' and 'Trust'. Thus, improved communication sensitises populations to the importance of pharmacovigilance, and generates increased awareness of the existence of reporting processes and systems, hence driving local data generation (see below). In addition, clear, transparent communication is an essential tool in building and maintain public trust in healthcare systems, increasing the likelihood of individuals to seek care, and collectively improving health outcomes. Efforts to improve communication between all pharmacovigilance stakeholders is therefore a fundamental aspect that will likely have great impacts on pharmacovigilance in LRSs.

Thirdly, there is a need to enable an increased local agency of pharmacovigilance data. The existence of locally-generated safety data is perhaps the most fundamental requirement to ensure the safety of a medical intervention in a population. As noted in the literature, the preponderance of global safety data is generated in HRSs. The ability to both access, and analyse data in a local-context is therefore essential to reduce medicines-related harm to populations in LRSs.

These themes emerged as priorities for pharmacovigilance in LRSs within the context of the COVID-19 pandemic. Although each of these themes had previously been identified as challenges for pharmacovigilance in LRSs (see **8.2**), whether they represented the highest priorities for pharmacovigilance advancement in LRSs outside of the pandemic context has not been investigated. Nevertheless, the identification of these themes during a global public health emergency provides insight into the immediate concerns amongst pharmacovigilance stakeholders when reacting to public health emergencies and periods of mass drug

administration/immunisation. These themes can be used to inform the responses to future public health emergencies in LRSs with regards to medicines safety.

42 Rapid Democratic Consensus Building

As noted above, capacity-building initiatives working in complex and multifaceted fields must be able to identify high-priority areas for focus to target their efforts and make the most efficient and effective use of their resources. This is of particular importance when there is an urgent need for the rapid sharing and generation of novel knowledge, such as in times of public health crises.

The action research approach adopted in this project (which built on TGHN's previous COVID-19 research activities), demonstrated an effective method of identifying high-priority targets for capacity-building initiatives. The cyclical process of planning, action, observation and reflection was followed at all stages, and each methodological 'step' (eg survey, workshop, working groups) represented one full cycle of the action research spiral. The success of this methodology in identifying immediate priorities was demonstrated across all stages of the research, including the high prevalence of knowledge gaps identified in the survey, the general agreement amongst workshop participants regarding the continued relevance of the top priories, and the iterative validation of these priorities via their re-emergence in the working group discussions.

In addition to its rapidity, the flexible nature of the process lends itself it to the determination of responses to urgent research questions and public health emergencies. The low resource-intensity of the method, and straightforward, pragmatic approach, makes this an ideal technique for adoption in LRSs.

The 'third person' participatory community approach to action research adopted in this project (see **11.3**) ensured that the research outcomes were led primarily by the participants,

and that they accurately portrayed contextual, as opposed to theoretical, challenges facing pharmacovigilance in LRSs.

Whilst nature of this research was participatory, it did not fall under the umbrella of Participatory Action Research (PAR). This was a consequence of the lack of participant involvement in the determination of the overarching research question and methodology. Nevertheless, the participant-led setting of research questions and methodologies seen amongst the working group project teams demonstrate the potential of the broader action research methodology to act as an enabler of PAR. Discussions of future working group activities should include an evaluation of the spontaneous emergence and value of the PAR approach.

At times, steps in this research were acknowledged to be potentially 'over rigorous' (see **25.7**). It is acknowledged that the rapidity of the consensus-gathering process could be increased via further streamlining of the methods discussed above, or via consideration of alternative processes. It is recommended that future researchers looking to emulate this methodology do so with a consideration of these factors, their individual timescales, and the urgency of their research.

In this research, a comparison of the research methodology with other, more 'traditional' consensus-building methods (eg Delphi, Nominal Group, etc) was not undertaken [174]. Indeed, it is acknowledged that the methodology outlined here features overlaps with both of these methods. Future research should seek to make comparisons between the 'Crowd Consensus' methods outlined in this research with these traditional consensus-gathering approaches.

43 The Knowledge Community Approach to Capacity Building

43.1 Community Evolution

The pharmacovigilance CoP went through a process of evolution and growth throughout the course of this project. This process is demonstrated visually in **Fig. 50**, drawing from Wenger et al's 'Degrees of Participation' model (se**e Fig. 9).**

The defining driver of community evolution was active participation in research activities. Prior to this research, GPV acted largely as a 'Community of Interest'. Members used the platform to access resources and remain informed of global pharmacovigilance activities, but there was no shared development of knowledge and ideas. The first element of collective knowledge generation was introduced by the survey, and the contribution of content experts from LRSs introduced the first element of participant agency to the research activities. Nevertheless, knowledge sharing between participants remained minimal, and community interactions limited to coordinator-participant as opposed to (participant-participant) exchanges.

By fostering the first measurable interactions between community members, the workshop established the first outline of what might be called a nascent CoP. The discussion allowed for the sharing of knowledge and experience between GPV members, and community members were extensively involved in the planning and implementation of the research. However, it was the launch of the working groups that finally saw sustained and regular interaction community members, and enabled unrestricted discussion and knowledge exchange to take place.

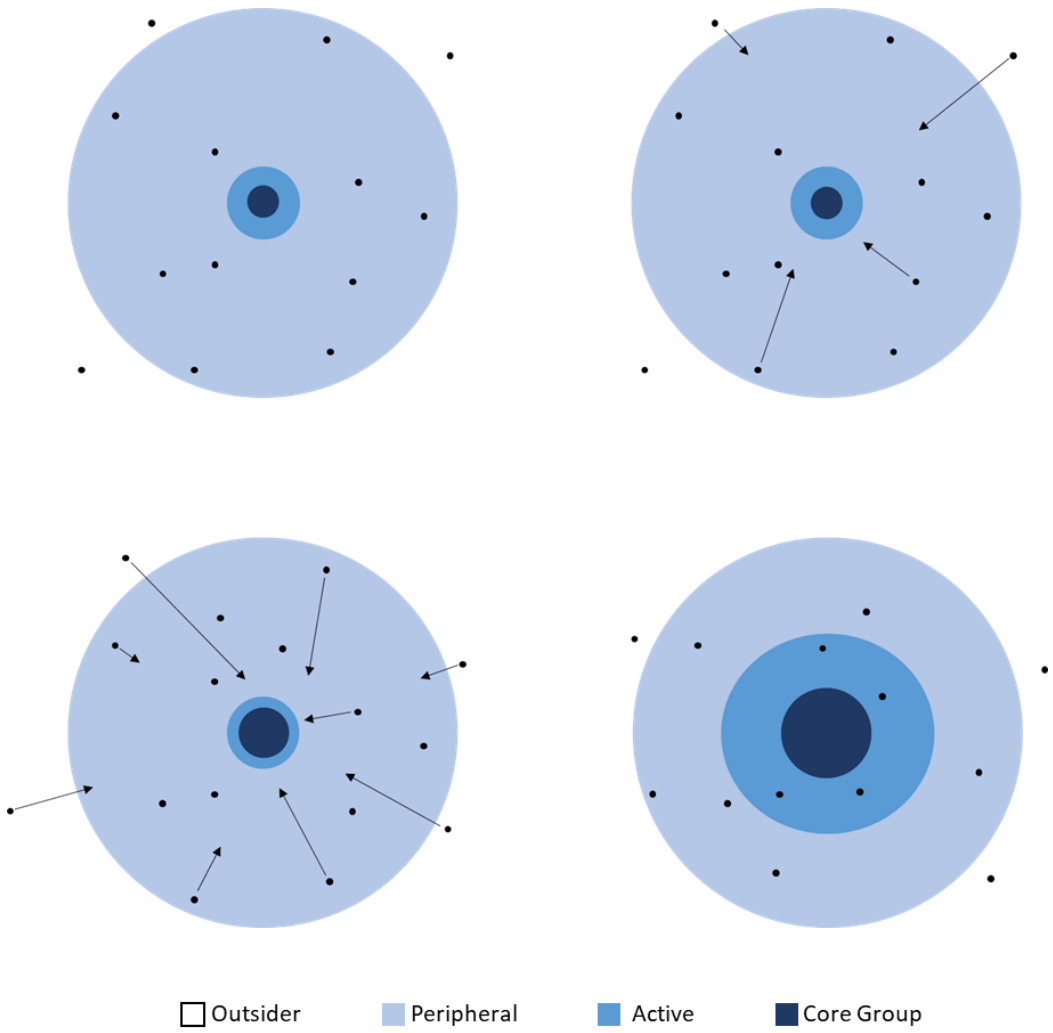


Figure 50: Evolution of the Pharmacovigilance CoP.

A) Prior to the Commencement of Research Activities: There was little active involvement of GPV members in GPV activities. The core group consisted solely of the GPV coordinators (researchers). Active involvement was minimal, although this space was occasionally occupied by members who submitted articles and blog posts. The peripheral space was extensive (Total GPV membership of approx. 3000) but largely inactive. The GPV membership more closely represented a 'Community of Interest' than a CoP

B) During the Survey: Core group activities were still restricted to the GPV coordinators. A small level of active participation has been maintained via the continued submission of articles and blogs. Greater involvement was seen at the peripheral level, as 'outsiders' (previous non-members of GPV) completed the survey and registered as members, and greater interest in GPV was generated amongst pre-existing members thanks to the active orchestration of research activities.

C) During the Workshop: The core group was expanded as the workshop chairs played a leading role in the planning and conduction of the research. There was still limited opportunity for an increase in active involvement at this point, although peripheral members that had been involved in both the survey and the workshop continued their centripetal trajectory.

D) Cessation of Research Activities: The Core Group had considerably expanded thanks to regular involvement in and leadership of GPV research activities by highly active members of the working groups. Greater active involvement was also seen in members with occasional input into working group activities, and involvement in group activities outside of the working group meetings.

43.1 Visualising a CoP

The fluidity of CoP boundaries has been acknowledged in the literature (see **11.4**). This was experienced first-hand in this project; the wide scope of the research made defining the 'limits' of the community difficult, and individual's fluctuation between the 'levels' of participation (see **Fig. 50**) made clearly quantifying individual participation challenging. In order to reflect the lack of definition between the boundaries of a CoP, it is proposed that future visualisations of CoPs clearly illustrate the lack of distinct boundaries between CoP levels. Two potential examples, 'Porous' and 'Nebulous' (both building on Wenger et al's model) are proposed in **Fig. 51**.

43.2 Value of the CoP Model to Pharmacovigilance in LRSs

The CoP model represented an effective strategy for fostering collaboration and enabling knowledge exchange/generation amongst pharmacovigilance stakeholders in LRSs. This was clearly demonstrated by both the high level of global participation in this project from a diverse range of pharmacovigilance stakeholders (see **39** and **40**), and the incidences of knowledge exchange/generation seen in the workshop, the working groups, and from contributions to GPV.

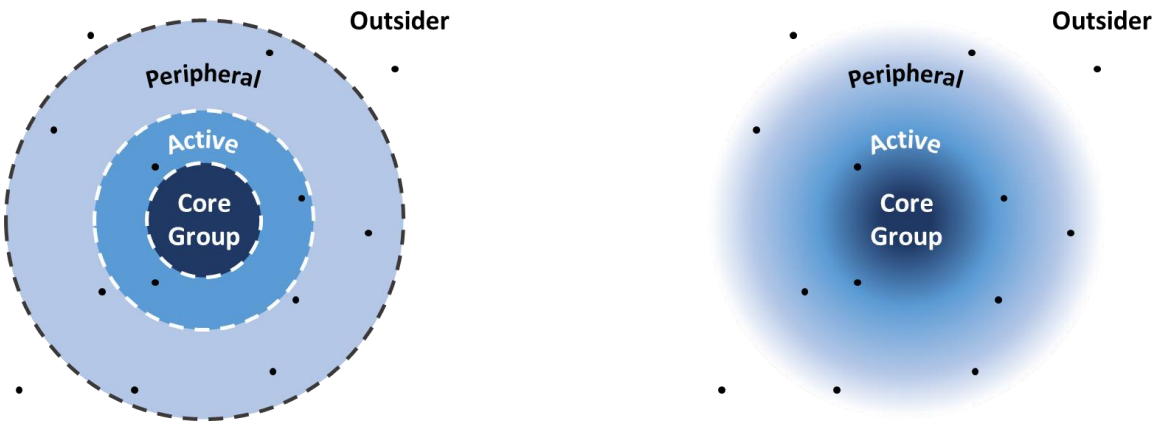


Figure 51: Porous (A) and Nebulous (B) visualisations of a CoP. Both examples illustrate the ill-defined spatial dimensions of the CoP, and lack of defined between the different levels of participation.

In addition, the CoP approach facilitated the successful identification of the highest priorities for pharmacovigilance in LRSs during the COVID-19 pandemic, where tools, education and guidance were needed. This is clearly demonstrated by the high level of consensus reached on the highest priorities identified above (see **41**). Even during priority-setting activities (survey validation, survey) with no participant-participant dialogue, participant contributions supported the evolution of the community, and ensured that future research activities were focussed and relevant to the community's aims.

The community only entered the initial stages of resource development during the course of this research. This was seen in the preparatory development of supporting documents for the research and intervention activities proposed by both working groups. In turn, this meant that the evaluation of such resources, and measurement of their potential impact on pharmacovigilance activities in LRSs, could not be undertaken. Nevertheless, the clear and ambitious research and resources planned by each working group illustrate the high potential of the CoP model to facilitate effective resource development.

The value of the CoP approach, at both the individual level to community participants, and at the field level to pharmacovigilance in LRSs, has not been investigated in this project. Due to the relatively short period of participant-participant interaction (approx. five months), it was deemed unlikely that such measurement would provide a reasonable indication value. Nevertheless, it is highly recommended that future knowledge-community initiatives seek to measure the value of their communities at both levels; the greater community value that can be demonstrated, the greater commitment to the communities activities by the participant, and the greater the potential impact of the community.

43.3 Beyond a Community of Practice?

Over the course of this research, it emerged that the evolving pharmacovigilance knowledge community was not operating within the traditional boundaries of the CoP model. This was driven by a reconsideration of the CoP component 'practice', which in the context of this work, had been broadly defined as 'Pharmacovigilance Activities in LRSs' (see **Fig. 2**).

As this research has confirmed (see **41**), pharmacovigilance is an incredibly diverse field. As such, the concept of an all-encompassing, shared 'pharmacovigilance practice' simply cannot exist. What pharmacovigilance 'involves' is heavily dependent upon the individual context; the approach to pharmacovigilance of a senior manager in a pharmaceutical company will be vastly different to that an HCP in a clinical setting or an academic in a university.

This exposes the challenges of applying a CoP model to such a diverse community. However, the successful evolution of a knowledge-based community, despite the lack of a fundamental element of a CoP, suggests that alternative models of learning may be more applicable. This was further revealed by the shift in strategy from knowledge exchange, to knowledge generation, within the working group activities (see **36.3**).

These practices imply the unconscious adoption of an alternative approach to learning to those previously discussed (see **4**). This is perhaps best described by the 'knowledge creation' metaphor

Paradigm	Standard/Classical	'Emerging'	Aspects seen in both Classical and Emerging paradigms
Example Learning Theory	Behaviourism/ Constructivism	Situated Learning	Examples seen in both individual and participatory theories
Metaphor of Learning	Acquisition	Participatory	Knowledge Creation
Unit of Analysis	Individual	Community	Community
Example Learning Loci	Classrooms/Schools	Communities of Practice	Innovative Knowledge Communities

Table 15: Comparison of three metaphors of learning.

of learning, as proposed by Paavola et al (see **Table 15**) [175]. In this theory, '*learning is seen as analogous to innovative approaches of inquiry where new ideas, tools and practices are created, and the initial knowledge is substantially enriched of significantly transformed during the process*' [176]. Hence, learning is not driven predominantly by participation in practice and the sharing of existing knowledge, but by participation in 'knowledge advancement'.

Haakarainen et al term the loci of such knowledge creation 'Innovative knowledge Communities' (IKCs) [176]. In '*Communities of Networked Expertise' (2004),* the authors acknowledge that such communities closely resemble CoPs in many ways, and propose that IKCs may even be considered a 'special form of CoPs'. However, a number of key distinctions between CoPs and IKCs are identified, some of which are summarised in **Table 16**.

These distinctions strongly suggest that the 'pharmacovigilance knowledge community' examined in this research may be more accurately described as an IKC than a CoP. Whilst this finding is considered important, two points must be noted; First, that regardless of whether the 'pharmacovigilance knowledge community' ultimately functioned as a CoP, application of the CoP model was a successful strategy in guiding community development in a capacity-building context

	Community of Practice	**Innovative Knowledge Community**
Main Focus	Creation of practices that allow the community to function routinely to meet its aims	Deliberate pursuit of social transformations to overcome constraints to knowledge creation
Community Design	Usually Emerge Spontaneously	Deliberately designed to facilitate knowledge creation, and support innovation
Nature of Leaning	Gradual accumulation of existing knowledge and practices	Systematic effort to seek and accumulate novel knowledge
Distribution of Knowledge	Hierarchical: more experienced 'old timers' transmit knowledge to 'newcomers'	Heterogeneous: New comers have valuable skills and can strengthen collective competencies

Table 16: Example distinctions between CoPs and IKCs. Adapted from Table 5, Communities of Networked Expertise, Haakarainen et al, 2004 [176] . Consultation of this reference for greater expansion on the relationship between CoPs and IKCs is highly recommended.

(see **43.2**); Second, that the activities of knowledge communities are by nature, dynamic. Knowledge communities may fluctuate between different 'classifications' of knowledge community depending on their activities, their participants, their aim, and their necessity. This has been both acknowledged in the literature, and experienced in in this research, evidenced by the community's evolution from a Community of Interest to a CoP/IKC [47, 176].

The full implications of the apparent metamorphosis of the pharmacovigilance knowledge community to an IKC have not been explored in this work. Nevertheless, this is not deemed to impact the findings of the research in any significant way, and only serves to highlight the dynamic nature of knowledge community research. Future research, whether building on the activities reported here or in other contexts, should further examine the relationship of the IKC model to knowledge community outcomes and capacity building initiatives. It is highly recommended that researchers seeking to undertake any form of group-based capacity-building research do so with an awareness of the knowledge creation metaphor of learning and IKC theory.

44 Sustainability

A core consideration of any capacity building initiative is that it should be sustainable, to ensure lasting value to the communities and populations it aims to benefit. The intrinsic qualities of the methodological approaches taken in this work, primarily the 'community driven' approach, offer an immediate potential for ensuring the continued advancement of research activities, and delivering a sustained impact to its participants; the assimilation of participants into the social knowledge-structure of the community, fosters a sense 'ownership', and hence greater commitment, towards the research. In turn, through increased subsequent involvement in, and co-ordination of, community activities (movement towards the 'core group', see **Fig. 50**), the role of community coordination is increasingly shared amongst community members, and this increase in collective social capital provides the impetus to facilitate the continuance of community activity.

Moreover, the high level of interest demonstrated in this research from the community members, discussed above (see **40** and **41**), highlights the obvious potential for the sustainability of these capacity building efforts. Nevertheless, it is acknowledged that despite this interest and involvement from knowledge community members, the researchers have remained key figures in many of the research activities discussed above (for example, co-ordinating working group meetings, see, also see). In order to ensure sustainability, it is essential that momentum of thesis research is not lost and that working group activities continue, with continued expansion of the CoP core group, and greater involvement in community co-ordination activities by community members. In order to adequately support these efforts, it is highly recommended that future funding be sought to support the maintenance and expansion of the GPV platform.

X Conclusions

This research set out to identify whether the membership of an online pharmacovigilance platform could operate as a CoP, to investigate whether the CoP could work together to identify the current priorities for pharmacovigilance in LRSs and develop resources to address these challenges, and to measure the impact of these resources on the work of those engaged in pharmacovigilance activities in LRSs.

Whether the GPV membership ultimately operated as a CoP is questionable. The ambitious scope of this research and the highly heterogeneous nature of the global pharmacovigilance community made adherence to the fundamental CoP framework unrealistic. In particular, the concept of a universal pharmacovigilance 'practice', which can be adopted by, and assimilate, all relevant pharmacovigilance stakeholders globally, is idealistic and impractical.

What is evident is that the membership functioned as a highly fluid and rapidly-evolving knowledge community. It is likely that an alternative model of knowledge community, an IKC, provides a more accurate description of the community's nature and design, however further investigation of this hypothesis is warranted. These findings highlight the pitfalls of clearly defining knowledge communities which can result from the dynamic nature of, the large number of different types of knowledge community, and the use of CoP as a catch-all term to define group-based knowledge activities.

Despite these uncertainties, the GPV membership effectively collaborated to identify the immediate priorities for pharmacovigilance in LRSs. This was enabled via the application of the CoP model, which guided community development to facilitate direct discussion between community members, and the iterative action research approach to consensus building, which ensured continuous critical reflection and discussion of ideas.

The priority-identification process confirmed that pharmacovigilance in LRSs is a highly complex and multidimensional field. Many of the challenges encountered are closely interlinked and their

effective resolution dependent on the targeting of multiple outcomes. In addition, there is a high prevalence of knowledge gaps in relation to many core aspects of pharmacovigilance amongst pharmacovigilance stakeholders in LRS. Greater training and education opportunities are needed to build pharmacovigilance capacity in these regions.

Improving communication between pharmacovigilance stakeholders, increasing local stakeholder agency in regards to local pharmacovigilance data, and ensuring the safety of medical interventions in vulnerable populations, particularly children and pregnant women, are key areas of focus where immediate action is required to improve pharmacovigilance outcomes in LRSs. Future capacity-building initiatives should seek to target these areas to ensure the greatest possible impact and efficient use of resources.

The implementation and impact of resources to address the priorities identified was not assessed, as the available timescales to complete resource development were restricted by the COVID-19 pandemic. Nevertheless, the clear strategic proposals for targeted interventions, developed by working group members, demonstrates the capacity of the CoP model to provide an effective platform for the collaborative, community-led development of such pharmacovigilance resources. Future efforts should endeavour to measure the value of community activities to both community members, and to the domain of interest.

Similarly, the ongoing nature of the projects' activities is a consequence of the iterative action research approach. The intrinsic momentum of the action research cycle continues to drive the knowledge community's activities and contributes to the sustainability of the capacity building efforts described above. It can therefore be concluded that the action research methodology provides a sustainable framework for initiatives seeking to build sustainable and participant-led pharmacovigilance capacity in LRSs.

Several unknowns remain and warrant further investigation. Primarily, this includes an assessment of the implementation of the community-developed interventions, and their impact upon

pharmacovigilance activities in LRSs. Similarly, the value of involvement in the knowledge community to the community members at an individual level has not been examined, which will be crucial to fostering greater community engagement. Additionally, whether approaches designed to enable knowledge generation as opposed to knowledge exchange are of greater value to capacity building initiatives, within both the field of pharmacovigilance and the wider umbrella of Global Health research, is yet to be discussed.

In conclusion, a knowledge community approach offers an effective strategy for initiatives seeking to improve pharmacovigilance activities in LRSs. The democratic, participant-led methodology provides direct solutions to many of the challenges facing pharmacovigilance in these regions, through the creation of inter-organisational and international networks, the holistic approach to participant contribution, and the collaborative approach to resource sharing and development. The adoption of a knowledge community approach either as the core element of pharmacovigilance capacity building initiatives, or as supporting element to guide such initiatives, has the potential to greatly improve pharmacovigilance capacity in LRSs, and reduce the inequities amongst pharmacovigilance stakeholders around the globe.

In the absence of alternative, clearly defined frameworks, or in incidences where the ultimate operation and outcomes of a fledging knowledge community are initially unknown, the CoP model provides an effective framework for nurturing knowledge-community development. Nevertheless, efforts to build pharmacovigilance capacity in LRSs should not focus purely on the exchange of existing resources and ideas, but on fostering the local generation of novel knowledge and approaches.

XI Limitations

Despite the rigorous conduct of this research, the findings have several limitations. Below, limitations to the overall thesis are discussed, whereas specific limitations to individual research activities have been identified throughout.

The geographic scope of this research (LRSs) was incredibly broad. This resulted in the generalisation of the findings to all LRSs globally, despite the enormous diversity across populations in these settings. Furthermore, efforts to ensure contextual clarity for participants relied upon a close equivalence of the terms 'LMIC' and 'LRS', and whilst in many contexts the application of both labels may overlap, complete equivalence cannot be assumed. It is acknowledged that the successful recruitment of a globally diversity population of participant's went some way towards mitigating these concerns. However, it must be acknowledged the findings of this research may not be applicable to all examples of a LRSs.

Many of the research activities received considerable input from participants in Africa. Whilst this contributed significantly to the high level of participation from LRSs, and in particular from a region with some of the lowest pharmacovigilance capacity globally, this may limit the value and applicability of the findings to LRSs outside of Africa. Future research concerning LRSs at a global level should seek to ensure equitable representation from all relevant regions.

Workload also represented a considerable constraint. The multifaceted nature of this research necessitated the researcher to adopt numerous additional roles and responsibilities. In particular, coordination of the two working groups required the effective adoption of a project management role, with a large number of associated responsibilities and time commitments. Given the conduction of these activities in tandem to the research activities, this was incredibly challenging. Future researchers looking to adopt a similar methodology should do so with a careful consideration of human resource capacity. The recruitment of a dedicated team of core researchers is highly recommended.

Due to researcher capabilities, all components of this research were conducted in English. This likely influenced the low levels of participation from non-Anglophone regions, and hence introduced an element of bias into the findings towards Anglophone regions. Some non-English language qualitative data was received in both the survey and the workshop, but this was limited. Future researchers should attempt to ensure their capacity to capture data from non-English speaking regions, to reduce the risk of research inequities arising/being perpetuated across language boundaries.

Whilst all components of this research were conducted in a highly rigorous and methodological manner, and whilst it is reiterated that 'less traditional', rapid approaches were taken to the qualitative elements in order to ensure the identification of, and action upon, the most immediate challenges facing pharmacovigilance in LRSs, it is acknowledged that the findings of this thesis could have been further enhanced by the conduction of 'traditional' in-depth qualitative research (in-depth interviews, focus group discussions, etc). Such activities would have been a logic next stage of the action research cycle, however the opportunity to conduct such research was restricted by available timeframes and workload constraints. It is highly recommended that such in-depth qualitative research is considered should the research cycle presented in this thesis continue, or should future researchers look to build on the consensus-building framework outlined in this thesis.

Part VI: Bibliography and Appendices

XII Bibliography

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XIII Appendices

Table of Contents

1 Literature Search Strategy 277
2 Rapid Resource Scoping Review Terms 279
3 Institutions that Developed Resources Identified in the Scoping Review 280
4 Validation Questionnaire 281
5 Validator Debriefing Document 300
6 CVI Values of Final Questionnaire Items 301
7 Pharmacovigilance in LRSs: Survey Validator Comments Discussion 303
8 Survey Questionnaire 306
9 Full Survey Priority Ranking Results 320
10 Workshop Guide 322
11 Workshop Poll 324
12 Workshop Discussion Transcript 328
13 Workshop Q&A Questions and Comments 337
14 Workshop Chat Box Comments 339
15 Working Group Registration Form 340

1 Literature Search Strategy

1. exp postmarketing surveillance/

2. (pharmacovigilance or "pharmaco-vigilance" or "drug surveillance" or "drug monitoring center*" or "drug monitoring centre*" or "drug monitoring program*" or "international drug monitoring" or "medicine* safety monitoring" or "adverse drug reaction* monitor*" or "adverse drug* reaction* report*").ti,ab.

3. "postmarketing surveillance".ti,ab.

4. "post marketing surveillance".ti,ab.

5. developing country/

6. low income country/

7. middle income country/

8. exp Africa/ or exp Asia/ or exp South America/ or exp Latin America/ or exp Central America/

9. (Africa* or Asia* or "South America*" or "Latin America*" or "Central America*").tw.

10. (lmic or lmics).tw.

11. "developing world".tw.

12. ((developing or "less$ developed" or "third world" or "under developed" or "middle income" or "low* income" or underserved or "under served" or deprived or poor$) adj (count$ or nation? or state? or population?)).tw.

13. "Lami countr*".tw.

14. (Afghan$ or Angola* or Bangladesh$ or Benin$ or Bhutan* or Bolivia* or Burkina Faso$ or Burm* or Burundi$ or "Cabo Verde*").sh,tw.

15. (Cambodia$ or Cameroon* or Central African Republic$ or Chad$ or Comoros or Congo* or "Cote d*" or Djibouti* or Egypt* or "El Salvador*" or Eritrea$ or Ethiopia$).sh,tw.

16. (Gambia$ or Gaza* or Georgia* or Ghana$ or Guinea$ or "Guinea-Bissau" or Haiti$ or Honduras* or India$ or Indonesia*).sh,tw.

17. (Kenya$ or Kiribati* or Korea$ or Kosovo* or Kyrgyz$ or Laos or Laot$ or Lesotho* or Liberia$ or Madagascar or Malagasy or Malawi$ or Mali$ or Mauritania$ or Micronesia* or Moldova* or Mongolia$ or Morocco* or Mozambi$ or Myanmar or Nepal$ or Nicaragua* or Niger$ or Nigeria$ or Pakistan$ or Papua New Guinea$ or Philippines or Rwanda$).sh,tw.

18. ("Sao Tome" or Senegal$ or Sierra Leone$ or Somalia$ or "Solomon Islands" or "Sri Lanka*" or Sudan$ or Syria* or Tajikistan$ or Tanzania$ or Timor$ or Togo$ or Tunisia* or Uganda$ or Ukraine* or Uzbek$ or Vanuatu* or Vietnam$ or "Viet nam*" or "West Bank" or Yemen$ or Zambia$ or Zimbabw$).sh,tw.

19. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20. 1 or 2 or 3 or 4

21. 19 and 20

22. 21

23. limit 22 to (english language and yr="2016 -Current")

2 Rapid Resource Scoping Review Terms

PV	LRSs	Resource
Postmarketing surveillance	developing countr*	Educational tool*
pharmacovigilance	low income countr*	e-Learning
drug surveillance	low-income countr*	"formal guidance"
drug monitoring center*	middle income countr*	guid*
drug monitoring centre*	middle-income countr*	"standard operating procedure*"
drug monitoring program	low middle income countr*	SOP
international drug monitoring	low-middle income countr*	tutorial*
medicine* safety monitoring	low and middle income countr*	template
adverse drug reaction* monitor*	Africa	tool*
adverse drug* reaction* report	Asia	video*
	South America	lecture*
	Latin America	seminar*
	Central America	webinar*
	lmic*	course
	developing world	
	Lami countr*	
	resource limited countr*	
	resource poor countr*	

3 Institutions that Developed Resources Identified in the Scoping Review

Institutions/organisations are displayed alphabetically by acronym.

Acronym	Organisation/Institution	Resources Identified (n)
ADP	The Access and Delivery Partnership	1
BfArM	Federal Institute for Drugs and Medical Devices (Germany)	1
BMJ	British Medical Journal	1
CIOMS	Council for International Organizations of Medical Sciences	1
DCVMN	Developing Countries Vaccine Manufactures Network	1
DIA	DIA	1
DSRU	Drug Safety Research Unit	1
EMA	European Medicines Agency	3
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.	1
Eu2P	European programme in Pharmacovigilance and Pharmacoepidemiology	1
FDA Ghana	Ghana Food and Drugs Authority	1
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use	1
ICMRA	International Coalition of Medicines Regulatory Authorities	1
IGMPI	Institute of Good Manufacturing Practices India	1
ISoP	International Society of Pharmacovigilance	1
LSHTM	London School of Hygiene and Tropical Medicine	1
MSH	Management Sciences for Health	1
NDA Uganda	National Drug Authority Uganda	1
PRA Zambia	Pharmaceutical Regulatory Authority Zambia (renamed the Zambia Medicines Regulatory Authority [ZAMRA] in 2013)	2
RPS	Royal Pharmaceutical Society	1
RRFA	Regulatory Resources for Africa	1
TGHN	The Global Health Network	3
UMC	Uppsala Monitoring Centre	2
USAID	United States Agency for International Development	3
WHO	World Health Organisation	10
-	Drug Office of the Department of Health, Hong Kong	1
-	MEDBOX	1
-	Netherlands Pharmacovigilance Centre Lareb	1
-	Unitaid	1

4 Validation Questionnaire

Priorities for Pharmacovigilance in Low and Middle-Income Countries during the COVID-19 Pandemic

Introduction

Thank you for taking the time to review this survey. This survey is being conducted by The Global Health Network (TGHN) as part of a larger project entitled 'Can Building a Community of Practice Improve Pharmacovigilance in Low and Middle-Income Countries'. This mixed methods action research project seeks to harness the membership of an existing online pharmacovigilance (PV) hub, globalpharmacovigilance.org (GPV) to work together in a 'community of practice' (CoP) on specific challenges facing PV in Low and Middle-Income Countries (LMICs).

It is well documented that PV activities have not been seen as a healthcare priority in developing countries. Despite good progress being made, PV capacity across LMICs in general remains weak, evidenced by poor awareness, low reporting numbers and a lack of adequate PV systems. Given the impact that the ongoing COVID-19 pandemic is having upon health systems globally, it is essential to ensure that PV systems in LMICs have the capacity to address both the novel, and exacerbated pre-existing challenges that they are now facing. In order to address this need, this survey is being developed with the primary aim of identifying exactly where the current knowledge gaps lie in relation to PV in LMICs during the pandemic. The results of the final survey will be presented to the CoP, and used to guide the focus of the group to work together to address that particular knowledge gap.

As this survey is being conducted as part of a larger project, it also seeks to gather demographic data and attitudes towards PV within the existing CoP. The precise aims of the survey are detailed below.

The final survey will be developed and deployed using the Jisc Online Surveys tool. It will be distributed via GPV mailing lists, social media accounts, and advertised directly on the GPV site. The survey will also be advertised across the wider TGHN network.

Survey Aims

Primary
1) To identify and prioritise PV knowledge gaps in LMICs, with specific relation to the COVID-19 pandemic.

Secondary
2) To gather demographic data in order to better understand the population that makes up the PV CoP
3) To assess attitudes towards PV within the PV CoP
4) To gather data on the usage and user experience of GPV

Population of Interest

Those involved in PV relevant to LMICs.

Validation Guide

- Questions from the survey are presented within the validation questionnaire below. I have also provided a copy of the survey itself. If you have not received this, please do not hesitate to let me know (ryan.walker@ndm.ox.ac.uk) and I will provide another copy. The survey-only document may provide a more readable view of the individual survey pages and give a more accurate understanding of the final layout and flow of questions.

- The survey consists mainly of 'tick box' type question responses. If this is not the case for a particular question, this will be identified in italics and square brackets, eg [*Free Text*], [*List*]

- Questions that are optional are indicated in the same way, [*Optional*]. All questions are considered compulsory unless indicated otherwise. Dependent questions are also highlighted in this way, eg [*If answer to X was X*].

- **For each question, unless specified otherwise, you are asked to indicate how relevant you think each question is to the survey aims** (Pg.1). This can be done using the numbered scale below each question, where 1 indicates 'Least Relevant', and 4 indicates 'Most Relevant'. For ease of understanding, the exact aim(s) that each question is trying to address will be listed next to the question. The aims can be referred to on page 1.

- If you have any additional thoughts on each question, including those related to readability, word choice, definitions etc, or if you wish to expand on your thoughts about question relevance, please don't hesitate to include them using the 'Comment' function, accessible using the 'Review' tab.

- The questionnaire can be completed digitally or printed out and completed physically. If completing physically, please write any additional thoughts on each question in the margin or on a separate piece of paper.

- For questions in the section 'Page 3: Priorities for Pharmacovigilance in LMICs During the COVID-19 Pandemic', the question frame, 'I need to know more about…' has been removed. The questions can be read in their entirety in the original survey document. This is both a formatting measure and to allow separate validation of the question framing. More details are found later in this questionnaire.

- Please feel free to contact me if you have any questions regarding the survey or this questionnaire - ryan.walker@ndm.ox.ac.uk.

The questionnaire begins
on the next page

Validation Questionnaire Page 1: Welcome!

Welcome to globalpharmacovigilance.org's (GPV) survey, **Priorities for Pharmacovigilance in Low and Middle-Income Countries During the COVID-19 Pandemic**. The primary aim of this survey is to understand which aspects of pharmacovigilance (PV) are perceived as the most important areas for improvement across low and middle-income countries (LMICs) during the COVID-19 pandemic. If you are based in these regions, we are especially interested in learning which aspects of PV you currently feel you need to know more about. We are also keen to hear about your day-to-day involvement with PV activities, and your experience of using GPV.

We would really appreciate you taking a moment to give us your thoughts and feedback. This survey consists of 17 questions and will take 5 to 10 minutes to complete.

Thank you in advance for you collaboration.

Please Note

The findings from this survey may be published in a report, a scientific journal and/or presented at a conference. Your identity will remain anonymous in all publications and presentations of the findings.

The information that you supply will be treated in accordance with the University of Oxford's Data Protection policy. This project has been reviewed and approved by Oxford Tropical Research and Ethics Committee (OxTREC). Reference number OxTREC 541-18. For any other queries please email ryan.walker@ndm.ox.ac.uk

No relevance scale has been included for this introductory text. If you have any comments on the introductory text, please provide them using the 'comment' function under the review tab.

If completing physically, please write any comments in the margin or on a separate piece of paper.

Validation Questionnaire Page 2: Your Experience of Pharmacovigilance

1. Which of the following describe(s) what the term 'Pharmacovigilance` means to you? Please select all that apply.

- The detection and assessment of drug-related adverse effects.
- The understanding and prevention of drug-related adverse effects.
- Improving the safety of all medical interventions including herbal medicines, blood products and medical devices.
- Encouraging the rational and effective (including cost-effective) use of all medical interventions
- Other*

*Please tell us what the term 'Pharmacovigilance' means to you [*Free Text Option*]

Survey Aims Targeted: Designed to act as a knowledge-test question, also addresses aim 3

Least Relevant ⟷ Most Relevant			
1	**2**	**3**	**4**
☐	☐	☐	☐

2. How frequently do you engage in pharmacovigilance activities* in your day-to-day role?
*(*For example, this may include reporting adverse drug reactions, collecting reports, analysing reports, disseminating medicines safety information, developing pharmacovigilance guidelines/SOPs, regulations etc.)*

- Every day
- More than once a week (but not every day)
- Once a week
- 2 or 3 times a month
- Once a month
- A few times a year
- Once a year
- Less than once a year

Survey Aims Targeted: 2

Least Relevant ⟷ Most Relevant			
1	**2**	**3**	**4**
☐	☐	☐	☐

3. To what extent do you agree or disagree with the following statement:

'Pharmacovigilance is relevant to my day-to-day role'

- Strongly Disagree
- Somewhat Disagree
- Neither Agree nor Disagree
- Somewhat Agree
- Strongly Agree

Survey Aims Targeted: 3

Least Relevant ◄——————————► Most Relevant			
1	**2**	**3**	**4**
☐	☐	☐	☐

Validation Questionnaire Page 3: Priorities for Pharmacovigilance in LMICs during the COVID-19 Pandemic

The following questions seek to assess the relevance of each pharmacovigilance 'theme' that has been included in the survey. In the survey, these themes are framed as follows:

'I need to know more about… [Theme]'

The themes are listed below, without the question frame.

Using the below scale, please indicate how relevant you believe each theme is to the survey's primary aim, 'To identify and prioritise PV knowledge gaps in LMICs, with specific relation to the COVID-19 pandemic'

4. General Vaccine Pharmacovigilance

Abbreviations:
PV = Pharmacovigilance
AEFI = Adverse Event Following Immunization
AESI = Adverse Event of Special Interest

	PV Topic/Area	Least Relevant ◄——► Most Relevant			
		1	2	3	4
4.a	Terminology used in vaccine PV.	☐	☐	☐	☐
4.b	Recognising AEFIs.	☐	☐	☐	☐
4.c	How to report AEFIs.	☐	☐	☐	☐
4.d	Different types of AEFI.	☐	☐	☐	☐
4.e	The clinical management of AEFIs.	☐	☐	☐	☐
4.f	Vaccine Associated Enhanced Disease	☐	☐	☐	☐
4.g	Recognising AESIs.	☐	☐	☐	☐
4.h	How to report AESIs.	☐	☐	☐	☐
4.i	'What other areas of vaccine pharmacovigilance are you interested in?' *[Optional] [Free Text]*	☐	☐	☐	☐

5. COVID-19 Vaccine Pharmacovigilance

Abbreviations:
AEFI = Adverse Event Following Immunization
AESI = Adverse Event of Special Interest

	PV Topic/Area	Least Relevant ◄——► Most Relevant			
		1	2	3	4
5.a	COVID-19 Vaccine AEFIs.	☐	☐	☐	☐
5.b	COVID-19 vaccine AESIs	☐	☐	☐	☐
5.c	Background rates of COVID-19 Vaccine AEFIs/AEFSs	☐	☐	☐	☐
5.d	Safety of administering COVID-19 vaccines with concomitant non-COVID-19 vaccines	☐	☐	☐	☐
5.e	Interactions of COVID-19 vaccines with other drugs	☐	☐	☐	☐
5.f	Safety of different COVID-19 vaccination schedules	☐	☐	☐	☐
5.g	Safety of 'mixing and matching' different COVID-19 vaccines	☐	☐	☐	☐
5.h	Falsified or substandard COVID-19 Vaccines	☐	☐	☐	☐
5.i	Analysis of COVID-19 vaccine safety data	☐	☐	☐	☐
5.j	'What other areas of COVID-19 vaccine pharmacovigilance are you interested in?' *[Optional] [Free Text]*	☐	☐	☐	☐

6. COVID-19 Vaccine Pharmacovigilance According to Patient Group

	PV Topic/Area	Least Relevant ◄——► Most Relevant			
		1	2	3	4
6.a	The safety of COVID-19 vaccination during pregnancy.	☐	☐	☐	☐
6.b	The safety of COVID-19 vaccination during lactation.	☐	☐	☐	☐
6.c	The safety of COVID-19 vaccination in the elderly.	☐	☐	☐	☐
6.d	The safety of COVID-19 vaccination in children/adolescents.	☐	☐	☐	☐
6.e	The safety of COVID-19 vaccination in those with existing co-morbidities	☐	☐	☐	☐
6.f	What other patient groups are you interested in? *[Optional] [Free Text]*	☐	☐	☐	☐

7. COVID-19 Therapeutics Pharmacovigilance

	PV Topic/Area	Least Relevant ◄——► Most Relevant			
		1	2	3	4
7.a	Common adverse drug reactions of COVID-19 therapeutics	☐	☐	☐	☐
7.b	Drug-drug interactions of COVID-19 therapeutics	☐	☐	☐	☐
7.c	The safety of traditional and complementary medicines that are being used in the management of COVID-19	☐	☐	☐	☐
7.d	Off-label/unlicensed use of therapeutics for COVID-19	☐	☐	☐	☐
7.e	Antibiotic use in COVID-19.	☐	☐	☐	☐
7.f	The safety of oxygen administration.	☐	☐	☐	☐
7.g	Substandard and falsified COVID-19 therapeutics	☐	☐	☐	☐
7.h	The safety of medical devices used in COVID-19 management (face masks, ventilators etc.)	☐	☐	☐	☐
7.i	What other areas of COVID-19 therapeutics pharmacovigilance are you interested in? *[Optional] [Free Text]*	☐	☐	☐	☐

8. Pharmacovigilance Systems and Communication during the Pandemic

Abbreviations:
PV = Pharmacovigilance

	PV Topic/Area	Least Relevant ◄——► Most Relevant			
		1	2	3	4
8.a	Sources of COVID-19 vaccine/therapeutic safety information.	☐	☐	☐	☐
8.b	COVID-19 related PV training.	☐	☐	☐	☐
8.c	New PV tools/reporting apps for COVID-19.	☐	☐	☐	☐
8.d	Ongoing global COVID-19 PV work and stakeholders.	☐	☐	☐	☐
8.e	Addressing COVID-19 vaccine safety misinformation	☐	☐	☐	☐
8.f	Addressing vaccine hesitancy	☐	☐	☐	☐
8.g	Continuing non-COVID-19 related PV activities during the pandemic	☐	☐	☐	☐
8.h	What else would you like to know about PV systems and communication during the pandemic? *[Optional] [Free Text]*	☐	☐	☐	☐

***For Survey Validators**: If you have any suggestions for any priority areas for improvement within PV in LMICS during the COVID-19 pandemic that are not mentioned above, please take the time to list them here:*

9. If you would like to expand on any of the responses you have given above, please take the time to do so here. *[Optional] [Free Text]*

Survey Aims Targeted: 1

Least Relevant ⟷			Most Relevant
1	**2**	**3**	**4**
☐	☐	☐	☐

10. Please tell us any further areas of pharmacovigilance which you think are a priority for improvement in your country during the COVID-19 pandemic, and if possible, explain why. *[Optional] [Free Text]*

Survey Aims Targeted: 1

Least Relevant ⟷			Most Relevant
1	**2**	**3**	**4**
☐	☐	☐	☐

Validation Questionnaire Page 4: Your Experience of globalpharmacovigilance.org

11. How frequently do you access globalpharmacovigilance.org?
- More than once a week
- Once a week
- 2 or 3 times a month
- Once a month
- A few times a year
- Once a year
- Less than once a year
- I have never accessed globalpharmacovigilance.org

Survey Aims Targeted: 4

Least Relevant ⟷ Most Relevant			
1	2	3	4
☐	☐	☐	☐

11.a. *[If answer to 11 is any answer excluding 'I have never accessed globalpharmacovigilance.org']* **Which of the following areas of the globalpharmacovigilance.org site have you accessed? Please select all that apply**

- Home Page
- 'Resources'
- 'Training, Education and Careers'
- 'Community'
- 'Conferences and Events'
- Unsure/Can't remember
- Other*

*If you selected Other, please specify *[Free Text option]*

Survey Aims Targeted: 4

Least Relevant ⟷ Most Relevant			
1	2	3	4
☐	☐	☐	☐

11.b. *[If answer to Q7 is any answer excluding 'I have never accessed globalpharmacovigilance.org']* **Has globalpharmacovigilance.org helped you in your research, studies or clinical role? Please tell us how.** *[Optional] [Free Text]*

Survey Aims Targeted: 4

Least Relevant ⟷			Most Relevant
1	2	3	4
☐	☐	☐	☐

12. What pharmacovigilance resources, tools or information would help you in your current role? *[Optional] [Free Text]*

Survey Aims Targeted: 4

Least Relevant ⟷			Most Relevant
1	2	3	4
☐	☐	☐	☐

Validation Questionnaire Page 5: General Information

13. Which of the following categories best describes your current role? *(If you work in more than one capacity, please select the category that best describes your primary role).*

- Nurse
- Physician
- Pharmacist
- Regulator
- Qualified Person for Pharmacovigilance
- Manufacturer
- Laboratory Scientist
- Pharmacovigilance Scientist
- Academic
- Student
- Other*

*If you selected Other, please specify *[Free Text option]*

Survey Aims Targeted: 2

Least Relevant ◄——► Most Relevant			
1	**2**	**3**	**4**
☐	☐	☐	☐

14. What type of establishment do you primarily work for?

- Hospital (Public)
- Hospital (Private)
- Community Health Centre/Facility
- Private Practice of GP
- Community Pharmacy
- Regulatory Body
- Government Research Organisation
- Public Health institute
- Non-Government Organisation
- Contract Research Organisation
- Pharmaceutical Company
- Journal
- University/College
- Other*

*If you selected Other, please specify *[Free Text option]*

Survey Aims Targeted: 2

Least Relevant ◄——► Most Relevant			
1	**2**	**3**	**4**
☐	☐	☐	☐

15. Do you work primarily in pharmacovigilance?

- Yes
- No

Survey Aims Targeted: 2

Least Relevant ⟷ Most Relevant			
1	**2**	**3**	**4**
☐	☐	☐	☐

15.a. [*If answer to Q.15 is 'Yes'*] **How long have you worked in pharmacovigilance?**

- Less than 1 year
- 1-5 years
- 6-10 years
- 11-20 years
- 20 + Years

Survey Aims Targeted: 2

Least Relevant ⟷ Most Relevant			
1	**2**	**3**	**4**
☐	☐	☐	☐

16. Which of the following describe(s) your level of training in pharmacovigilance? Please select all that apply.

- I have never had any formal pharmacovigilance training
- I have completed an online course(s) on pharmacovigilance
- I was taught about pharmacovigilance at university
- I have attended a face-to-face training course(s) on pharmacovigilance
- I have taught/conducted a training course(s) on pharmacovigilance
- Other*

*If you selected Other, please specify *[Free Text option]*

Survey Aims Targeted: 2

Least Relevant ⟷ Most Relevant			
1	**2**	**3**	**4**
☐	☐	☐	☐

17. Which country do you work in?
If you work in more than one country, please select the country in which you work primarily

[UN Countries List, dropdown box]

Survey Aims Targeted: 2

Least Relevant ⟷ Most Relevant			
1	**2**	**3**	**4**
☐	☐	☐	☐

17.b *[If answer to Q.17 is a High-Income Country, as classified by the World Bank]* **If you do not work primarily in an LMIC, please briefly describe your interest in pharmacovigilance in LMICs** *[Optional] [Free Text]*

Survey Aims Targeted: 2

Least Relevant ⟷ Most Relevant			
1	**2**	**3**	**4**
☐	☐	☐	☐

Validation Questionnaire Page 6: Workshop and Working Group Invitation

Thank you for participating in this survey. The information you have provided will be used to guide future research into the improvement of pharmacovigilance capacity in LMICs during the COVID-19 pandemic. We plan to present the results of this survey via a virtual workshop in due course, at which time attendees will be invited to join a working group with the aim of addressing the identified research priorities. If you wish to be kept up-to-date on the survey findings and upcoming workshop plans, please let us know:

- Yes
- No

[If answer is 'Yes']
- Name

- Email Address

No relevance scale has been included for this closing text. If you have any comments on the closing text, please provide them using the 'comment' function under the review tab.

If completing physically, please write any comments in the margin or on a separate piece of paper.

End of validation questionnaire.
Thank you for your time.

5 Validator Debriefing Document

Topics for discussion

Method of asking Q4 (question frame) *Does 'I need to know more about' really assess priorities and knowledge gaps?*	
Repetition of patient group section (4.c) for therapeutics (4.d) *Should this section be repeated for therapeutics? Does survey length suffer?*	
Use of Jargon *eg AEFI etc*	
Timing/Length *How long did it take you to complete? What are your thoughts on the survey length?*	
Do any questions need completing? *Has the respondent missed any questions?*	
Do any questions need justification? *Do you disagree with any of the respondent's answers?*	
Any other thoughts *Ask the respondent if they have anything they'd like to add*	
Demographic Information *Location, Profession*	

6 CVI Values of Final Questionnaire Items

Page	Question Number	(I-CVI)
	Introduction	n/a
	Survey Aims	n/a
	Population of Interest	n/a
	Validation Guide	n/a
Page 1	Welcome Text	n/a
Page 2	1	1
Page 3	Instructions	n/a
Page 4	2.a	0.9
	2.b	1
	2.c	1
	2.d	1
	2.e	0.9
	2.f	0.8
	2.g	0.9
	2.h	1
	2.i	0.9
	2.j	1
	2.k	0.9
	3.a	1
	3.b	0.9
	3.c	0.9
	3.d	0.9
	3.e	0.8
	3.f	0.9
	3.g	0.8
	3.h	1
	3.i	1
	3.k	1
	4.a	1
	4.b	1
	4.c	0.9
	4.d	1
	4.e	1
	4.f	1
	4.g	1
Page 5	5.a	0.9
	5.b	0.9
	5.c	0.8
	5.d	0.9

Page	Question Number	(I-CVI)
Page 5 (Cont.)	5.e	0.9
	5.f	0.8
	5.g	0.9
	5.h	0.9
	5.i	1
	5.j	1
	6.a	1
	6.b	0.9
	6.c	0.8
	6.d	1
	6.e	1
	6.f	0.9
	6.g	0.9
	6.h	1
	6.i	1
	6.j	0.9
	7	1
	8	1
Page 6	9	0.8
	9.a	0.9
	9.b	1
	10	1
Page 7	11	1
	12	1
	13	0.9
	13.a	1
	14	1
	15	1
	16	1
	16.a	0.9
Page 8	Workshop and WG Invitation	n/a
Page 9	Completion Page	n/a
S-CVI/Ave		0.94

7 Pharmacovigilance in LRSs: Survey Validator Comments Discussion

Data

Many of the comments reiterated challenges raised in the literature review. One of these themes was challenges relating to pharmacovigilance data, in particular local data generation and local data access. Concerns regarding data generation provided additional insights into the determinants of low AE reporting rates discussed in the literature (see **8.2**), which included discussions of poor awareness and a lack of motivation to report:

> '*There is little or no incentive to report [AEs]. Many HCP's don't know what to report, and will only report directly to the drug company, or only report in incidences of death*'
>
> **Academic, Caribbean.**

This raises several considerations. Firstly, the lack of 'incentive' to report AEs could imply either a lack of moral incentive to report, of suggest the expectation of a 'reward' for reporting ('reward' in this incidence may not only be conceptualised as a financial incentive, but could include feedback from data collectors etc). In both cases, the need for 'incentive' suggests that HCPs do not consider reporting AEs to be integral part of their everyday practice. This was explicitly raised by a separate content expert:

> '*Many pharmacists in my country view pharmacovigilance as a work target, rather than a necessary part of everyday practice*'
>
> **Hospital Pharmacist/Pharmacoepidemiologist, East Africa.**

Secondly, the comments suggest a lack of awareness amongst HCPs of appropriate reporting channels, reporting requirements and an understanding of when to report an AE. Reporting exclusively to pharmaceutical companies may contribute to data silos (see below). It is also possible that only reporting incidences of death suggests that HCPs do not consider reporting non-serious (or even non-fatal) AEs to be necessary or worthwhile, although it is likely that other factors (eg the overburdening of HCPs in LRSs and a lack of time to report, see **8.2**) contribute to this.

These considerations highlight the critical need to instil pharmacovigilance as an integral part of healthcare practice during the training and education of HCPs in LRSs. Improved awareness of the importance of pharmacovigilance activities, and greater knowledge of reporting systems and processes, are in turn likely to ameliorate attitudes to reporting and increase reporting habits, driving the generation of local pharmacovigilance data.

Data access also emerged as a challenge for pharmacovigilance in LRSs. In particular this concerned the inexistence of local data, and the lack of data sharing between relevant stakeholders (data silos, see above):

> '*In LMICs, I find often missing [sic] is a good background database of medical conditions which can be used to compare against a cluster of AEFIs and to be able to calculate attributable risk.*'
>
> **Academic, Southeastern Asia**

A lack of background data has a fundamental impact on the ability to estimate reaction rates and the relative risk of a medical intervention. Crucially, whilst background data frequently exists for populations in HRSs, this information is not generalizable to populations in LRSs (see **8.2**). This lack of access to local data presents a major bottleneck to the conduct of fundamental pharmacovigilance activities in LRSs at both the regulatory level, and in the conduction of local

pharmacovigilance research, greatly hampering the ability to make evidence-based decisions regarding medicines safety.

Concerns regarding a lack of background data overlap with the concerns regarding underreporting discussed above. Nevertheless, the generation of background data depends upon well-defined rigorous methodologies, as opposed to the spontaneous reporting of ICSRs. This emphasises the need to improve pharmacovigilance research capacity, and the ability to conduct robust epidemiological studies, in LRSs. In turn, this will ensure the policy makers have access to high quality, locally relevant data to inform decisions regarding medicines safety.

Knowledge and Attitudes

As discussed above, limited knowledge of reporting channels and poor attitudes towards AE reporting amongst HCPs are suggested to be a significant contributing factor to low AE reporting rates in LRSs. In addition, general unfamiliarity with the term 'pharmacovigilance' was noted in some LRSs:

> *'Pharmacovigilance is not a well understood term in the pacific islands and we have promoted the 'Problems with Medicines' concept…. [In relation to the questionnaire] You would need to clarify what pharmacovigilance is before you will get an accurate estimation of time used for pharmacovigilance activities'*
>
> **National Principal Pharmacist, Australia and New Zealand/Melanesia**

This raises important concerns regarding the use of jargon and technical terms when seeking to implement medicines safety activities in regions with little-to-no previous pharmacovigilance activity. Capacity building initiatives in such regions should take place following a consideration of the need to balance harmonisation and education regarding technical terms with local pharmacovigilance literacy levels. However, challenges regarding health literacy expand past purely safety related terminology:

> *'Health literacy is very low in many LMICS. This can damage vaccine confidence in consumers, especially those of a lower socioeconomic status'*
>
> **Academic, Southeastern Asia**

This demonstrates the wider educational and training needs in which the challenges of building pharmacovigilance capacity in LRSs are embedded. This highlights the need of pharmacovigilance stakeholders to take a holistic approach to pharmacovigilance education and training by delivering information about wider healthcare concerns as well.

Resources

Resources also emerged as a key theme from the content experts comments. Given this research's focus on LRSs, this is unsurprising, however, the comments offered further insight intro particular resources of concern, or greatest need.

> *'The support group [sic] doing disease epidemiology are often not considered part of the pharmacovigilance team, but they are important.'*
>
> *'Do not forget those involved with the back end of the health system: epidemiologist, the health policy drafters, financing, IT units, the regulators. Plus, do not forget the communicators, spokesperson [sic]. Those involved in transmitting pharmacovigilance*

information following, say, a vaccine AEFI might be a midwife in the community and may not be in our radar for pharmacovigilance.'

Academic, Southeastern Asia

The above comments identify a need for a greater focus on human resources. In particular, these comments suggest the need to engage stakeholders at all levels of the pharmacovigilance spectrum, particularly those that may not be considered 'primary actors' within the pharmacovigilance sphere.

In addition, 'financing' was raised as a challenge for pharmacovigilance activities in LRSs. This is consistent with the literature (see **8.2**), and gives further credence to calls for ring-fenced pharmacovigilance budgets within LRSs, and a greater focus on pharmacovigilance research by research funding organisations.

8 Survey Questionnaire

Priorities for Pharmacovigilance in Low and Middle-Income Countries during the COVID-19 Pandemic

Survey Question

Which aspects of PV are a priority for improvement in LMICs during the COVID-19 Pandemic?

Survey Aims

Primary
1) To identify and prioritise PV knowledge gaps in LMICs, with specific relation to the COVID-19 pandemic.

Secondary
2) To gather demographic data in order to better understand the population that makes up the PV CoP
3) To assess attitudes towards PV within the PV CoP
4) To gather data on the usage and user experience of GPV

Population of Interest

Those involved in PV relevant to LMICs.

Notes on Formatting in this Document

This survey consists mainly of 'tick box' type question responses. If this is not the case for a particular question, this will be identified in italics and square brackets, eg [*Free Text*], [*List*]

Questions that are optional are indicated in the same way, [*Optional*]. All questions are considered compulsory unless indicated otherwise. Dependent questions are also highlighted in this way, eg [*If answer to X was X*].

Survey Questionnaire Page 1: Welcome!

Welcome to **globalpharmacovigilance.org**'s (GPV) survey, **Priorities for Pharmacovigilance in Low and Middle-Income Countries during the COVID-19 Pandemic**. The primary aim of this survey is to understand which aspects of pharmacovigilance (PV) are seen as the most important areas for improvement across low and middle-income countries (LMICs) during the COVID-19 pandemic. If you are based or have an involvement in PV in these regions, we are especially interested in learning which aspects of PV you currently feel you need to know more about. We are also keen to hear about your day-to-day involvement with PV activities, and your experience of using GPV.

We would really appreciate you taking a moment to give us your thoughts and feedback. This survey consists of 16 questions and will take 10-15 minutes to complete.

Thank you in advance for your collaboration.

Please Note

The findings from this survey may be published in a report, a scientific journal and/or presented at a conference. Your identity will only be requested if you wish to join a follow-up workshop and/or working group, and will remain anonymous in all publications and presentations of the findings.

The information that you supply will be treated in accordance with the **University of Oxford's Data Protection policy**. This project has been reviewed and approved by Oxford Tropical Research and Ethics Committee (OxTREC). Reference number OxTREC 541-18. For any other queries please email **ryan.walker@ndm.ox.ac.uk**

Survey Questionnaire Page 2: What Does Pharmacovigilance Mean to You?

1. Which of the following describe(s) what the term 'Pharmacovigilance` means to you? **Please select all that apply.**

- The detection and assessment of drug-related adverse effects.
- The understanding and prevention of drug-related adverse effects.
- Improving the safety, quality and efficacy of all medical interventions including herbal medicines, blood products and vaccines.
- Encouraging the rational and effective (including cost-effective) use of all medical interventions
- Other*

* Please tell us what the term 'pharmacovigilance' means to you [*Free Text Option*]

Survey Questionnaire Page 3: Priorities for Pharmacovigilance in Low and Middle-Income Countries during the COVID-19 Pandemic

The following questions focus on topics within the field of pharmacovigilance that have been identified as areas in need of improvement during the COVID-19 pandemic. They are grouped into the following topics:

- General Vaccine Pharmacovigilance
- COVID-19 Vaccine Pharmacovigilance
- COVID-19 Vaccine Pharmacovigilance According to Patient Group
- Pharmacovigilance of Medicines Used to Manage COVID-19
- Pharmacovigilance Systems and Communication During the Pandemic

For each topic, you are asked to **identify whether you feel you need to know more about different areas of pharmacovigilance within that topic**. At the end of this section (Page 5) there is the option to expand on your responses and identify any additional aspects of pharmacovigilance that you believe are relevant, if you wish.

Survey Questionnaire Page 4: Vaccines

Do you feel that you need to know more about the areas of pharmacovigilance listed below? For each area, **please indicate your level of agreement as to whether you think that you need to know more about that topic.**

2. General Vaccine Pharmacovigilance

Abbreviations:
PV = Pharmacovigilance
AEFI = Adverse Event Following Immunisation
AESI = Adverse Event of Special Interest

"I need to know more about…"

	PV Topic/Area	Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree
2.a	Terminology used in vaccine PV					
2.b	Recognising AEFIs					
2.c	How to report AEFIs.					
2.d	Different types of AEFI					
2.e	Clinical management of AEFIs					
2.f	Vaccine Associated Enhanced Disease (VAED)					
2.g	Recognising AESIs					
2.h	Case definitions of AESIs					
2.i	How to report AESIs					
2.j	Causality assessment of AEFIs/AESIs					

2.l What other areas of general vaccine pharmacovigilance are you interested in? *Note: The next question discusses COVID-19 vaccine pharmacovigilance in greater detail. [Optional] [Free Text]*

3. COVID-19 Vaccine Pharmacovigilance

Abbreviations:
AEFI = Adverse Event Following Immunisation
AESI = Adverse Event of Special Interest

"I need to know more about…"

	PV Topic/Area	Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree
3.a	Common COVID-19 vaccine AEFIs					
3.b	COVID-19 vaccine AESIs					
3.c	Background rates of COVID-19 Vaccine AEFIs/AESIs					
3.d	Safety of administering COVID-19 vaccines alongside non-COVID-19 vaccines					
3.e	Interactions of COVID-19 vaccines with other drugs					
3.f	Safety of different COVID-19 vaccination schedules					
3.g	Safety of 'mixing and matching' different COVID-19 vaccines					
3.h	Falsified or substandard COVID-19 vaccines					
3.i	Analysis of COVID-19 vaccine safety data.					

3.k What other areas of COVID-19 vaccine pharmacovigilance are you interested in? *[Optional]*
[Free Text]

4. COVID-19 Vaccine Pharmacovigilance According to Patient Group

"I need to know more about the safety of COVID-19 vaccination in..."

	PV Topic/Area	Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree
4.a	Pregnancy					
4.b	Breastfeeding					
4.c	The Elderly					
4.d	Children/adolescents					
4.e	People with existing co-morbidities					
4.f	People who are immunosuppressed					

4.g What other patient groups are you interested in? *[Optional] [Free Text]*

Survey Questionnaire Page 5: Medicines, Systems and Communication

Do you feel that you need to know more about the areas of pharmacovigilance listed below? For each area, **please indicate your level of agreement as to whether you think that you need to know more about that topic.**

5. Pharmacovigilance of Medicines Used to Manage COVID-19

" I need to know more about…"

	PV Topic/Area	Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree
5.a	Common adverse drug reactions of COVID-19 medicines					
5.b	Drug-drug interactions of COVID-19 medicines.					
5.c	Safety of traditional and complementary medicines that are being used in the management of COVID-19					
5.d	Off-label/unlicensed use of medicines for COVID-19					
5.e	Antibiotic use in COVID-19					
5.f	Safety of oxygen administration					
5.g	Substandard and falsified COVID-19 medicines					
5.h	Safety of medical devices used in COVID-19 management (face masks, ventilators etc.)					
5.i	Safety of COVID-19 medicines in special patient groups (pregnancy, elderly etc.)					

5.j What other areas of COVID-19 medicine pharmacovigilance are you interested in? *[Optional] [Free Text]*

6. Pharmacovigilance Systems and Communication during the Pandemic

Abbreviations:
PV = Pharmacovigilance

"I need to know more about…"

	PV Topic/Area	Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree
6.a	Sources of COVID-19 vaccine/medicine safety information					
6.b	COVID-19 related PV training					
6.c	New PV tools/reporting apps for COVID-19					
6.d	Ongoing global COVID-19 PV work and stakeholders					
6.e	Addressing COVID-19 vaccine safety misinformation					
6.f	Addressing vaccine hesitancy					
6.g	Continuing non-COVID-19 related PV activities during the pandemic					
6.h	How to effectively communicate COVID-19 vaccine/medicine safety information					
6.i	How to access COVID-19 vaccine/medicine safety data					

6.k What else would you like to know about PV systems and communication during the pandemic? *[Optional] [Free Text]*

7. If you would like to expand on any of the responses you have given to the questions on this page (page 5) or the previous page (page 4), **please take the time to do so here.** *[Optional] [Free Text]*

8. Please tell us any further areas of pharmacovigilance which you think are a priority for improvement in your country during the COVID-19 pandemic, **and if possible, explain why.** *[Optional] [Free Text]*

Survey Questionnaire Page 6: Your Experience of globalpharmacovigilance.org

9. How frequently do you access globalpharmacovigilance.org?

- More than once a week
- Once a week
- 2 or 3 times a month
- Once a month
- 2 or 3 times a year
- Less than twice a year
- I have never accessed globalpharmacovigilance.org

9.a. *[If answer to Q9 is any answer excluding 'I have never accessed globalpharmacovigilance.org']* Which of the following areas of the globalpharmacovigilance.org site have you accessed**? Please select all that apply:**

- Home Page
- 'Resources'
- 'Training, Education and Careers'
- 'Community'
- 'Conferences and Events'
- Unsure/Can't remember
- Other*

*If you selected Other, please specify *[Free Text option]*

9.b. *[If answer to Q9 is any answer excluding 'I have never accessed globalpharmacovigilance.org']* Has globalpharmacovigilance.org helped you in your research, studies or clinical role? **Please tell us how.** *[Optional] [Free Text]*

10. What pharmacovigilance resources, tools or information would help you in your current role? *[Optional] [Free Text]*

Survey Questionnaire Page 7: General Information

11. For how long have you been involved in pharmacovigilance?
'Involvement' can include paid or pro bono work, consultancy, research, post-graduate study etc.

- I do not have an involvement in pharmacovigilance
- Less than 1 year
- 1-5 years
- 6-10 years
- 11-20 years
- 20 + Years

11.a. In the past 12 months, how frequently have you engaged in pharmacovigilance activities?

For example, this may include reporting adverse drug reactions, collecting reports, analysing reports, disseminating medicines safety information, developing pharmacovigilance guidelines/SOPs, regulations etc.

- More than once a week
- Once a week
- 2 or 3 times a month
- Once a month
- 2 or 3 times in the past 12 months
- Less than 2 times in the past 12 months

12. To what extent do you agree or disagree with the following statement:

'Pharmacovigilance is relevant to my work'

- Strongly Disagree
- Somewhat Disagree
- Neither Agree nor Disagree
- Somewhat Agree
- Strongly Agree

13. Which of the following categories describes your current role? If you work in more than one capacity, **please select all that apply.**

- Nurse
- Doctor
- Pharmacist
- Dentist
- Regulator
- Qualified Person for Pharmacovigilance
- Vaccine/Drug Manufacturer
- Laboratory Scientist
- Pharmacovigilance Scientist
- Ministry of Health Official

- Academic/Researcher
- Student
- Other*

*If you selected Other, please specify *[Free Text option]*

14. What type of establishment do you work for? **If you work for more than one establishment, please select all that apply.**

- Hospital (Public)
- Hospital (Private)
- Community Health Centre/Facility
- Private Practice or GP
- Community Pharmacy
- Non-pharmacy Drug Dispensing Outlet
- Regulatory Body
- Government Ministry
- Government Research Organisation
- Public Health institute
- Immunisation Program
- Non-Government Organisation
- Pharmaceutical Company
- Contract Research Organisation
- University/College
- Journal
-Other*

*If you selected Other, please specify *[Free Text option]*

15. Have you been involved in COVID-19 clinical trials, vaccine development or post-marketing safety studies?

- Yes
- No

16. Which country do you work in? If you work in more than one country, **please select the country in which you work primarily**

[UN Countries List, dropdown box]

16.a *[If answer to Q.18 is a High-Income Country, as classified by the World Bank]* **If you do not work primarily in an LMIC, please briefly describe your interest in pharmacovigilance in LMICs** *[Optional] [Free Text]*

Survey Questionnaire Page 8: Workshop and Working Group Invitation

Thank you for participating in this survey. The information you have provided will be used to guide future research into the improvement of pharmacovigilance capacity in LMICs during the COVID-19 pandemic. We plan to present the results of this survey via a virtual workshop in due course, at which time attendees will be invited to join a working group with the aim of addressing the identified research priorities. If you wish to be kept up-to-date on the survey findings and upcoming workshop plans, please let us know:

- Yes
- No

[If answer is 'Yes']
- Name

- Email Address

Survey Questionnaire Page 9: Final Page

Your responses to this survey have been submitted.

If you need a formal record of your submission, please use the following details:

[Completion Receipt]

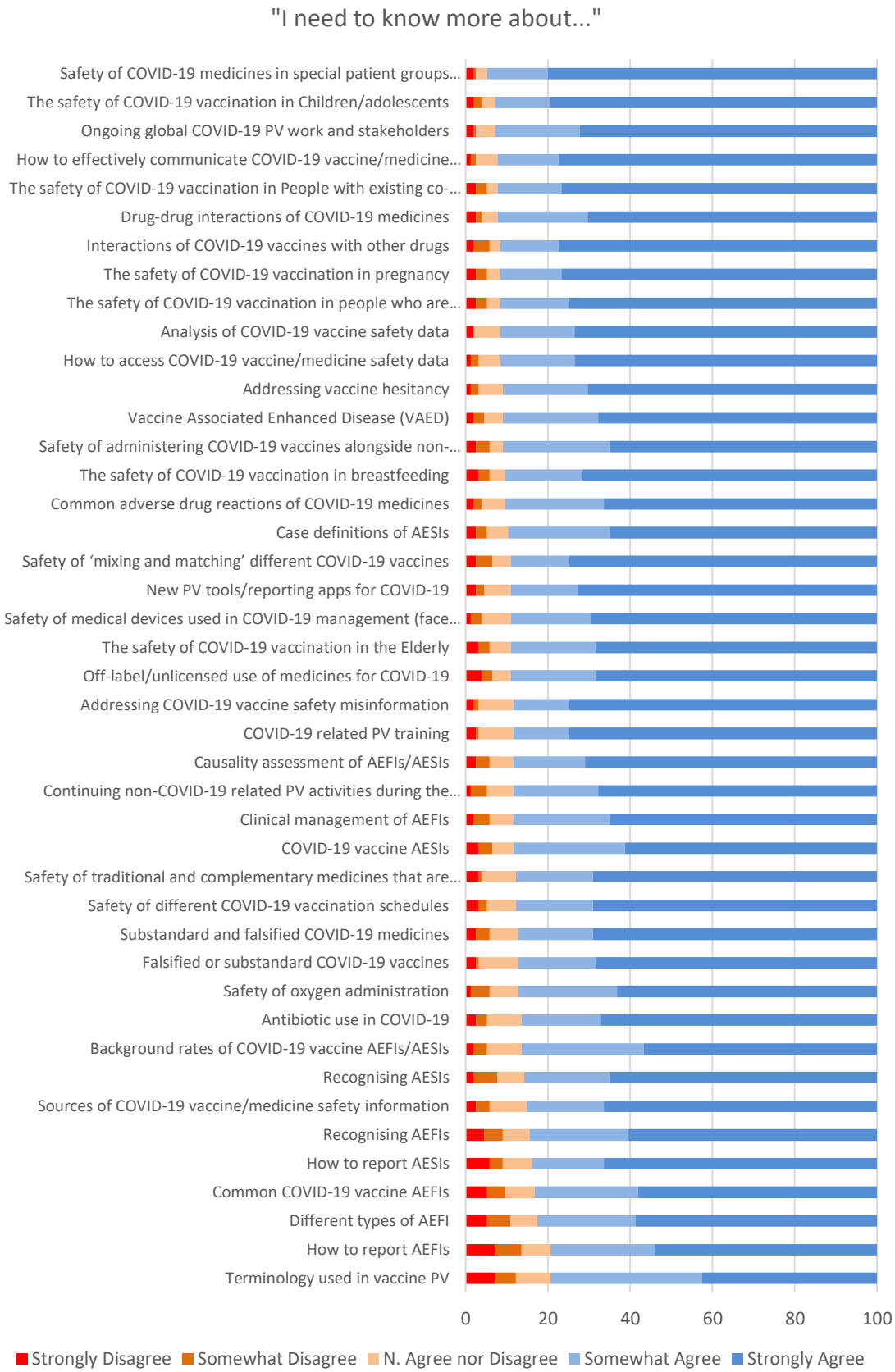
[Responses Download]

This survey is now complete.

Thank you for your time!

9 Full Survey Priority Ranking Results

See following page for ranked list of items in full.



Rank	Item
1	Safety of COVID-19 medicines in special patient groups (pregnancy, elderly etc.)
2	The safety of COVID-19 vaccination in Children/adolescents
3	Ongoing global COVID-19 PV work and stakeholders
4	How to effectively communicate COVID-19 vaccine/medicine safety information
5	The safety of COVID-19 vaccination in People with existing co-morbidities
6	Drug-drug interactions of COVID-19 medicines
7	Interactions of COVID-19 vaccines with other drugs
8	The safety of COVID-19 vaccination in pregnancy
9	The safety of COVID-19 vaccination in people who are immunosuppressed
10	Analysis of COVID-19 vaccine safety data
11	How to access COVID-19 vaccine/medicine safety data
12	Addressing vaccine hesitancy
13	Vaccine Associated Enhanced Disease (VAED)
14	Safety of administering COVID-19 vaccines alongside non-COVID-19 vaccines
15	The safety of COVID-19 vaccination in breastfeeding
16	Common adverse drug reactions of COVID-19 medicines
17	Case definitions of AESIs
18	Safety of 'mixing and matching' different COVID-19 vaccines
19	New PV tools/reporting apps for COVID-19
20	Safety of medical devices used in COVID-19 management (face masks, ventilators etc.)
21	The safety of COVID-19 vaccination in the Elderly
22	Off-label/unlicensed use of medicines for COVID-19
23	Addressing COVID-19 vaccine safety misinformation
24	COVID-19 related PV training
25	Causality assessment of AEFIs/AESIs
26	Continuing non-COVID-19 related PV activities during the pandemic
27	Clinical management of AEFIs
28	COVID-19 vaccine AESIs
29	Safety of traditional and complementary medicines that are being used in the management of COVID-19
30	Safety of different COVID-19 vaccination schedules
31	Substandard and falsified COVID-19 medicines
32	Falsified or substandard COVID-19 vaccines
33	Safety of oxygen administration
34	Antibiotic use in COVID-19
35	Background rates of COVID-19 vaccine AEFIs/AESIs
36	Recognising AESIs
37	Sources of COVID-19 vaccine/medicine safety information
38	Recognising AEFIs
39	How to report AESIs
40	Common COVID-19 vaccine AEFIs
41	Different types of AEFI
42	How to report AEFIs
43	Terminology used in vaccine PV

10 Workshop Guide

Timeline

	12.45 – 13.00	*Chairs/presenters to Join to make final checks and preparations.*
Presentations	**13.00 - 13.05**:	Workshop to go live at 13.00. Introduction to workshop to be given by ISoP Africa EC member.
	13.05 – 13.20	[Researcher #2] to present on GPV. Presentation to be introduced by ISoP Africa EC member.
	13.20 – 13.25	Q&A in relation to [Researcher #2]'s presentation. Chaired by ISoP Africa EC member.
	13.25 – 13.40	[Researcher #1] to present on the priorities for PV in LMICs Presentation to be introduced by ISoP Africa EC member.
	13.40 - 13.50	Q&A in relation to [Researcher #1]'s presentation. Chaired by ISoP Africa EC member.
Discussion	**13.50 – 15.00**	Open discussion chaired by ISoP Africa EC. **See items for discussion below**
	Approx. 14.48	Discussion to pause whilst **Zoom Poll** is run.
	14.55 – 15.00	Closing remarks and end of workshop, chaired by ISoP Africa EC member.

Questions to Guide the Open Discussion

- Do you think the pharmacovigilance themes highlighted in the presentation are relevant in your setting? Do they apply in your country, your region, or your place of work?

- Have you had any experience in any of the areas highlighted in the presentation? Have you encountered problems, or successes? What worked, and what didn't?

- What do you think can be done to address the pharmacovigilance challenges identified?

- The survey was conducted 4 months ago - do you think these priorities identified are still relevant, or are there now different concerns?

- What are the current challenges facing pharmacovigilance in your region? How do you think these can be addressed?

- This research has focussed on COVID-19-related pharmacovigilance. Do you think this is currently a primary concern of PV? Are there other priorities?

- Are there particular vaccines or medicines that you are interested in?

- Have you conducted pharmacovigilance/safety related research during the pandemic? Would you like to discuss your findings with us?

- Have you developed a pharmacovigilance/safety related resource, SOP, protocol, training aid etc. that you would be interested in sharing with us working in PV in LMICs? If so, please don't hesitate to get in touch after the workshop!

If participants mention a specific theme, eg 'I think the safety of vaccines in pregnancy is a priority', *probe*:

- Can you expand on that? Have you had experienced something in your work related to this? How do you think we can address this? Etc.

11 Workshop Poll

In-Workshop Poll

Text included in holding slides and read out to participants

The first question lists the top ten pharmacovigilance priorities identified in Global Pharmacovigilance's recent survey. The priorities have been grouped but are not ranked in any order.

From this list, please select THREE elements of pharmacovigilance that you believe to be the current highest priorities at this point in the COVID-19 Pandemic, where support, training and guidance are needed.

Please carefully select THREE (and only THREE) responses to this question, as Zoom will not cap your number of responses.

This workshop seeks to gather consensus on the current pharmacovigilance priorities in Low and Middle – income Countries. If you are based in a High-Income Country but have experience working in, supporting, or a personal interest in pharmacovigilance activities in LMICs then we warmly welcome your contribution. If you do not consider yourself to have an interest in pharmacovigilance activities in LMICs, we kindly ask that you do not complete this poll at this time.

Poll Text

1) From this list, please select THREE elements of pharmacovigilance that you believe to be the current highest priority at this point in the COVID-19 Pandemic where support, training and guidance are needed.

- The safety of COVID-19 VACCINATION in Children/adolescents
- The safety of COVID-19 VACCINATION in pregnancy
- The safety of COVID-19 VACCINATION in people with existing co-morbidities
- The safety of COVID-19 VACCINATION in people who are immunosuppressed
- Interactions of COVID-19 VACCINES with other drugs
- Analysis of COVID-19 VACCINE safety data
- Ongoing global COVID-19 PV work and stakeholders
- How to effectively communicate COVID-19 vaccine/medicine safety information
- Drug-drug interactions of COVID-19 MEDICINES
- The safety of COVID-19 MEDICINES in special patient groups (pregnancy, elderly etc.)

2) Do you feel that the themes listed above are currently relevant to your setting?

- Strongly Disagree
- Somewhat Disagree
- Neither Agree nor Disagree
- Somewhat Agree
- Strongly Agree

Post-Workshop Poll

Page 1: Welcome!

Welcome to globalpharmacovigilance.org's (GPV) survey, Workshop Poll: Priorities for Pharmacovigilance in Low and Middle-Income Countries during the COVID-19 Pandemic. This survey has been developed following technical difficulties in the recent Global Pharmacovigilance/ISoP Africa Chapter online workshop 'What are the Priorities for Pharmacovigilance in LMICs during the COVID-19 Pandemic?'. The aim of this survey is to understand which of the pharmacovigilance (PV) priorities that were discussed in the workshop are the highest priorities for PV in low and middle-income countries (LMICs) right now.

You have received this survey because you indicated that you were unable to view the in-workshop poll. Please do not share this link.

This survey consists of 4 questions and will take less than 5 minutes to complete.

Thank you in advance for your collaboration.

Please Note

The findings from this survey may be published in a report, a scientific journal and/or presented at a conference. Your identity has been requested only to ensure that there is no duplication of results from the in-workshop poll, and will remain anonymous in all publications and presentations of the findings.

The information that you supply will be treated in accordance with the University of Oxford's Data Protection policy. This project has been reviewed and approved by Oxford Tropical Research and Ethics Committee (OxTREC). Reference number OxTREC 541-18. For any other queries please email ryan.walker@ndm.ox.ac.uk

Page 2: Priorities for Pharmacovigilance in Low and Middle-Income Countries during the COVID-19 Pandemic

The workshop and subsequent poll/survey seeks to gather consensus on the current pharmacovigilance priorities in LMICs. If you are based in a High-Income Country but have experience working in, supporting, or a personal interest in pharmacovigilance activities in LMICs then we warmly welcome your contribution.

If you do not consider yourself to have an interest in pharmacovigilance activities in LMICs, we kindly ask that you do not complete this survey at this time.

Q1) From this list, please select THREE elements of pharmacovigilance that you believe to be the current highest priority at this point in the COVID-19 Pandemic where support, training and guidance are needed. *(Required, only 3 options selectable)*

- The safety of COVID-19 VACCINATION in children/adolescents
- The safety of COVID-19 VACCINATION in pregnancy
- The safety of COVID-19 VACCINATION in people with existing co-morbidities
- The safety of COVID-19 VACCINATION in people who are immunosuppressed
- Interactions of COVID-19 VACCINES with other drugs
- Analysis of COVID-19 VACCINE safety data
- Ongoing global COVID-19 PV work and stakeholders
- How to effectively communicate COVID-19 vaccine/medicine safety information
- Drug-drug interactions of COVID-19 MEDICINES
- The safety of COVID-19 MEDICINES in special patient groups (pregnancy, elderly etc.)
-

Q2) Do you feel that the themes listed above are currently relevant to your setting? *(required)*

- Strongly Disagree
- Somewhat Disagree
- Neither Agree nor Disagree
- Somewhat Agree
- Strongly Agree

Page 3: General Information

Please provide your name and email address.

Your identity has been requested only to ensure that there is no duplication of results from the in-workshop poll, and will remain anonymous in all publications and presentations of the findings.

- Name *(required)*
- Email (please provide the email address with which you registered to the workshop) *(required)*

Page 4: Thank You!

Thank you for completing this survey. As discussed in the workshop, your responses will be used to determine the areas of focus for future pharmacovigilance working groups. Global Pharmacovigilance will provide an update on the poll results and an invitation to join the working groups in the coming weeks.

Page 5: Survey Complete

Your responses to this survey have been submitted.

If you need a formal record of your submission, please use the following details:

[Completion receipt]

[My responses]

This survey is now complete.

Thank you for your time!

12 Workshop Discussion Transcript

Transcript begins just over an hour into the workshop proceedings (01:02:25) at the commencement of the workshop discussion period, following a presentation on the chairing organisation, a presentation on the TGHN/GPV platforms, a presentation on the outcomes of the survey, and a question and answer period following the presentations.

Discussion Participants

Chairs/Panellists
- Chair #1 – *ISoP Africa Chapter EC*
- Chair #2 – *ISoP Africa Chapter EC*
- Chair #3 – *ISoP Africa Chapter EC*
- Chair #4 – *ISoP Africa Chapter EC*
- Researcher #1 – *TGHN/GPV*
- Researcher #2 – *TGHN/GPV*

Participants
- Doctor, Hospital, Nepal
- Managing Director, Pharmacovigilance Consultancy, UK
- Ministry of Health Official, Ministry of Health, Kenya
- Head of Pharmacovigilance and Clinical Trials, NMRA, Zimbabwe

Transcript

Workshop Time: 01:02:25

Chair #3: Perfect. So thank you so much [Chair #2] for taking us through the second part of this webinar that we've had with the Global Health Network team. For now I'd like to introduce everyone else to the third part, or the last part, of our webinar today and we wanted to take this opportunity and open up the discussion and just allow people to, you know, give their reactions, give their comments with regards to the presentations that have been provided today, yeah? So as we open, we invite you to share your thoughts on the themes identified in the survey, if there any relevant - if at all any of the themes that were discussed were relevant in your setting, do they apply to what you do in a day-today in your country, in your region - yeah just so that we can get to know which, area really identified with you, mainly because we want to know, you know, this would be an opportunity for us to help you in troubleshooting, some of the problems, some of the successes that have been identified, especially within our region, as we are part of the low-medium income countries or LMIC countries, and therefore we expect, and we have been able to see that some of the challenges, some of the things that have been discussed, they are cutting across different regions, so we really want to take this opportunity and welcome you, so please just start sharing your thoughts with us, please use the Q&A, the chat box, they're all available to you - and we just welcome you to just start telling us what's really been working for you, with regards to the discussions for today, some of the thematic areas that have been highlighted to you, yeah. So, the floor is yours participants, please, let us know what you feel. Your reactions. We can also be - also will be monitoring for guys, who are raising their hands, as you can see I've just demonstrated just down here on your toolbox, you can be able to start - You can use any of the tools that are available to you. All right. Okay, so we have two hands raised. Can I ask [Technical Advisor, The Philippines] to unmute [themselves] and tell us your reactions? [Technical Advisor, The Philippines]? All right, if we can't hear from [Technical Advisor, The Philippines], can I ask [Doctor, Hospital, Nepal]?

Doctor, Hospital. Nepal [Participant]: Hello?

Chair #3: Hi we can hear you.

Doctor, Hospital, Nepal [Participant]: Good evening from Nepal, I am [name]. Currently I'm working as an investigator for clinical trial in Nepal. We are doing a phase three clinical trial study

and since pharmacovigilance – we see in our phase four. So my concern was like, what are the - what are the different priorities with COVID vaccination with other different tropical diseases, like we are facing a lot of issues in phase three, where we are vaccinating people and seeing different other COVID-like illnesses, based on when there is peak of influenza as well, so we are seeing a lot of co-infections, so how the vaccine will respond, even during the winter season with influenza and other respiratory virus is also one of my concerns for the vaccine pharmacovigilance. Pharmacovigilance as our previous speaker said, is prioritized based on different headings, like he told about pharmacovigilance in pregnancy, in autoimmune diseases, different other medical interactions, drug interactions but my concern was, what is the pharmacovigilance in COVID-19 vaccine with other tropical diseases as well? Like in Nepal, we are seeing a lot of COVID illnesses, with different co-infections, we have seen with HIV, AIDS, we have seen with influenza, we are seeing with typhoid. So how are we people prioritizing this pharmacovigilance in terms of COVID-19 vaccine with other tropical diseases? Thank you.

Chair #3: All right, thank you [Doctor, Hospital, Nepal]. I think I'll ask again, [Technical Advisor, The Philippines] if you have - you'd like to take this opportunity and ask your question? I think you can unmute yourself. Alright, then I don't think [Technical Advisor, The Philippines] is there, I think we'll go next to [Managing Director, Pharmacovigilance Consultancy, UK], [Managing Director, Pharmacovigilance Consultancy, UK] we will give you the opportunity to ask the question directly to the panellists, thank you.

Managing Director, Pharmacovigilance Consultancy, UK [Participant]: Thank you, I just was asking what structured cooperation, collaboration, is in place in Africa to share PV workload and encourage PV learning from experience, so that is my question. The reason for this question is, I have been involved in another collaboration with manufacturing, global manufacturing, which is focused on human performance, to get better structured cooperation, collaboration, team-working globally between manufacturers, and, the outcome of that is to develop guiding principles, because, although we have a lot of differences cultures, languages regulations, what we all have in common is, we are all humans. Human performance is central and that can be a part of the structure of your guiding principle and community of practice, so very happy I'll share that information with [Researcher #1], and [they] can then circulate that to the African chapter. Meanwhile, if you'd like to respond to the question now –and to - that would be very helpful, thank you.

Chair #3: Alright, thanks [Managing Director, Pharmacovigilance Consultancy, UK] I think I'd like to ask, [Research #2] and [Researcher #1], to answer the first two questions that have been raised by their participant and then after that we'll be able to see about the questions in the Q&A box and also the comments section. As we carry along, right? Thank you.

[Researcher #2 encounters technical difficulties with internet connectivity]

Researcher #1: Very good question [Managing Director, Pharmacovigilance Consultancy, UK], I - again I don't want to play hot potato with the question, but I think perhaps the best people to answer it would be the ISoP Africa chapter, so I don't know if [Chair #2] or [Chair #1], if you have any thoughts on what [Managing Director, Pharmacovigilance Consultancy, UK] said? Just as specifically his question relates to Africa.

Chair #2: [Chair #1] or [Chair #4] do you want to take that, I didn't hear the question I didn't quite get it.

Chair #4: Maybe if I can just repeat and [Managing Director, Pharmacovigilance Consultancy, UK] I don’t know if I got it well, but [Managing Director, Pharmacovigilance Consultancy, UK] is asking, is there any corporations or collaborations within Africa in regard to pharmacovigilance? Is that right?

Chair #3: Yes, yes that's exactly what he asked.

Chair #4: Okay, so I'll try to answer the best I can. So yes there've been a bit – there've been collaborations, ongoing collaborations on strengthening pharmacovigilance within the region and one key collaboration has been through the African Medicines Regulatory Harmonization project which was looking at strengthening regulatory systems within the different economic regional blocs, for example, the East African Community, the intergovernmental - I mean that is IGAD, the intergovernmental authority on – sorry, I've forgotten the name in full, but IGAD and we have like also some regions, the [unintelligible] regions where a lot of harmonization has been going on, of their systems, and in particular for pharmacovigilance. I'll take an example of East African Community, and the IGAD community, where through the harmonization in collaboration that has been going on they've been - adoption in harmonization of pharmacovigilance systems like guidelines, tools, and, for example, looking at the electronic reporting tools, Kenya was among the first countries that implemented these and through this, and through this, there's been sharing of information and countries like Tanzania, Rwanda visiting and also, like training with Kenya capacity building, just to see how this is working, and then they able to implement the same in their countries. We've had like Zimbabwe, which also is one of the countries that was able to work with Kenya and implement this, also system on them. And also we appreciate that, with the coming up of the African medicines regulatory authority, AMA, so there are processes in place that are going on, to see how data that is being collected from pharmacovigilance can be synchronized and used for decision making within the region, and just as [Managing Director, Pharmacovigilance Consultancy, UK] said rightly, we cannot work in isolation and that's why this harmonization process - activities have been going on, and we also have collaborations also with other outside the region and, like, for example, there is a currently ongoing collaboration between Kenya, Tanzania, Ethiopia, Rwanda, through an EDCTP supported grant where there's been a lot of work on strengthening of pharmacovigilance within this region, and also through the same there is also the PAVIA project which has Tanzania, Ken- I mean Tanzania Ethiopia, Nigeria and I think, Eswatini, which are also collaborating and strengthening these systems, so I believe this is a good starting point for Africa, and once the systems become mature and the collaborations are well established, it will make our work easier, since the patients are kind of the same, the data you're collecting and the information that is being [unintelligible] can be utilized to just ensure that, the patients are benefiting from the information that is PICs and their health is taken care of. Thank you.

Chair #3: Thank you, thank you, [Chair #4] for that. Because I see, we are running short of time, there are some reactions that I'd like to read and maybe elicit more discussion so I've seen a comment from [Regulatory Officer, NMRA, Ghana] and [they] says, the Med Safety App by the FDA Ghana, has been very instrumental to healthcare workers and the general public in reporting ADRs, we also have [Senior Program Officer, Intergovernmental Organisation, Uganda], 'I believe the key issue facing LMICs is safety communication. There is some lack of hesitance and confidence in communicating safety information, thereby creating an environment of lack of trust between the ministries, regulators and the public has a ripple effect, we end up having vaccine hesitance, infodemics - I'm assuming information - becomes unmanageable', we also see the same reaction presented in Kenya through [Pharmacovigilance Specialist, Hospital, Kenya], [they] say that as a lot of this, the reporting issue, 'there is a lot of hesitancy in reporting, where the healthcare workers feel that they do not get any feedback, a lot has been changing, especially during this COVID-19 pandemic. There are also increasing interest in PV in - in the general hospitals', yeah? So the themes apply, so we also have [Research Officer, University, Nigeria] who says 'the themes apply in Nigeria, especially the safety of COVID-19 vaccinations in pregnancy, as women need to be monitored for the safety of the vaccines on pregnancy outcomes' - wow that's, that's amazing. So, thank you very much for sending your comments your questions. Maybe this, this would be the best time to also jump in and maybe ask everyone in general, because some of the - actually [Researcher #1]'s presentation basically just analyses, or it presents to us the survey that was conducted about four months ago and currently, based on the reactions that we're getting from people, and we just need to know more, especially from people working in the industry – do you think the current priorities

that were highlighted, are they, are they still relevant today – now we're in 2022, we're getting quite a lot of areas getting access to the COVID-19 vaccine. So, what are your reactions, what's going on in that direction? Are we are we getting to know - is, there is an issue COVID vaccine PV becoming an issue, is it awareness in your area? What do you think?

Researcher #1: [Chair #3] I don't know if you mind if I just jump in for a second but yeah I think you're absolutely right and some of the comm- the comments that we're getting in the chat, and some of what people have contributed have been really, really interesting so far. I know we had, we had [Doctor, Hospital, Nepal] discussing their concerns with clinical trials and the safety of vaccination with infectious diseases and it'd be really interesting to hear, if anyone else on the call has had any similar experiences, or if, that they found that to be a concern, because in the survey we identified vaccination, with people with existing co-morbidities as a priority, but narrowing that down, exactly what areas of that are the greater concern is really interesting to hear about and with infectious diseases again it's a really interesting area. So it'd be fantastic to hear if anyone else on the call has had that experience, if they've experienced anything like that in their in their clinical practice, but also, as you mentioned we're getting a lot of comments about communication and feedback and one [unintelligible] in relation to feedback of safety information to healthcare workers on the ground, but we're also getting comments that this affects reporting hesitancy as well, so again if you've experienced that in your country or in your pharmacovigilance practice, it'd be fantastic to hear from you on that front.

Chair #3: Ok thanks [Researcher #1] for picking that up. So there is a question that has been raised by [Ministry of Health Official, Ministry of Health, Kenya] in the Q&A box and [they] say, 'is it possible to revise the current AEFI reporting tools to be comprehensive and capture the various age cohorts and populations, as outlined by [Researcher #1]?' [Ministry of Health Official, Ministry of Health, Kenya] I'm assuming you're referring to the Kenya AEFI reporting tools, right? Maybe if you could raise your hand and expand that further. That would be good. Additionally-

[Ministry of Health Official, Ministry of Health, Kenya]: Yes, thank-

Chair #3: Thanks [Ministry of Health Official, Ministry of Health, Kenya]

[Ministry of Health Official, Ministry of Health, Kenya]: Yes, thank you everyone, and thank you [Chair #3] I think yes in the context of the current AEFI system that we're using in Kenya, is it possible that we could have these various cohorts and populations captured, that - once this data, or all this information is collected, then it's easier to identify where are the pregnant mothers, as well the adolescent, the elderly yeah that's what [unintelligible], thank you.

Chair #3: Thanks [Ministry of Health Official, Ministry of Health, Kenya], unfortunately [Chair #4] I'm going to throw this question to you as [identifiable information redacted], do you have any comments? Towards [Ministry of Health Official, Ministry of Health, Kenya]?

Chair #4: That is something that can be looked on, but also to appreciate that the form is adopted, from the WHO global form, so sometimes again, it becomes difficult because this data is pulled into one global database, so breaking it down into different, maybe components that are not aligned to the one that we submit can be a bit of a challenge, but we take note of the question and probably in the future with the discussion from the vaccines program we can see, if this is something that can be explored.

Chair #3: All right, thanks [Chair #4] for that. There's a very interesting question from one anonymous attendee and they asked, do you think they use of real-world data has a role to play in COVID-19 vaccination safety monitoring and in PV, and how - how do you think it would be relevant, so the question, one second, is do you think real world data has a role to play with COVID-19 vaccine safety monitoring, and if it is, how do you think it's going to be relevant, thank you.

Chair #2: I may jump in here. Yeah so I want to say that I almost want to say, yes to that and to say that I think, at least from the postmarketing or post-introduction perspective, much of the work that we do in pharmacovigilance is really collecting real world data, if you look at something like the passive reporting systems that many of our countries, many countries, implement or have in place and how that data is collected - yeah I would say that that is collecting real world data right? And if done well you know, that real world data really gives you evidence of what is happening in real life with the medicines that are put out there. How are people day to day using these medicines and how is it affecting people, so I think, to a very large extent, I would say yes that's almost I would say, that's almost the crux of the post-introduction part of pharmacovigilance work, and then just moving, moving on to the just speaking a bit about the, the COVID - specifically about the COVID work that [Researcher #1] has also shown and the priorities, I'm looking at something like the safety of COVID-19 vaccination in pregnancy and to say that, I haven't at the moment seen a lot of papers coming out from LMIC countries, but I do know that there are quite a number of studies – data that has been collected in other parts of the country, that have shown to a large extent that there aren't any serious risks, that, out there, at least that have been picked so far, and I think that is really one area that, you know, we could also focus in LMICs, to get that kind of real-world data in what's happening, recognizing that there are a number of countries in Africa that are currently doing one form of COVID-19 vaccine monitoring or the other, I know in Nigeria, there is cohort event monitoring, Ghana has done cohort event monitoring, Ethiopia has done cohort event monitoring, Kenya - so many countries are currently doing cohort event monitoring, and other forms of active surveillance to collect data, cohort event monitoring, so I think it really presents an opportunity for countries to identify data related to pregnancy, now probably a number of countries have also approved, I don't know how many countries in Africa have approved the vaccination in children, I think it also presents us an opportunity to collect that kind of data in real life, to see how these vaccines are working, and I think it does remain an area of priority, or it should remain an area of priority, that people can focus on and, hopefully, you know we can do more studies we can collect - put additional effort to collect data in those areas that can inform policy decisions related to the vaccines, over.

Chair #3: All right. Thank you, thank you [Chair #2] for that explanation. [Chair #3 experiences technical difficulties, Chair #2 takes up discussion moderation]

Chair #2: All right, sure, thank you, [Chair #3] sure, so let me, let me go through the Q&A to see if there's any questions, in the meantime [Researcher #1], I just wanted to check with you and to see if there is any particular area that you think that you would want us to touch upon, while, during this session?

Researcher #1: Thanks [Chair #2] but no it's, it's completely up to the participants and, and it'd be just great to hear more about what people think are the current concerns in their region or in their country, or their workplace, whether it relates to these priorities or not, and if there are there are greater concerns if there are, concerns relating to anything that are not necessarily safety related that'd be fantastic to hear those well. I just wanted to make a point on the back of that and question, and thank you and [Chair #4] for you fantastic answers to it, I can't remember who submitted the question sadly, but I think it was someone with an anonymous profile, but I just wanted to as [Researcher #2] said, sort of throw the question back to them if they're still on the call, and ask them what they thought about your responses and perhaps ask them maybe even to elaborate a little bit on what they mean by real world data, because I think [Chair #4] expanded on, on that very well, but are they interested in things like gathering data from social media and so on and so forth, so it'd be great if perhaps they could elaborate a little bit more on that.

Chair #2: Thanks [Researcher #1], and, if I remember it was an anonymous person, but if the anonymous person would want to turn on their mics we're happy to let you speak and to clarify the question if it wasn't adequately responded to.

Researcher #1: If we haven't got any responses at the moment I'll just address some of the questions in the Q&A if that's okay.

Chair #2: Yes, please go ahead fantastic.

Researcher #1: So there is a very pertinent question that is 'why were there no questions included in the survey that were related to COVID-19 vaccine efficacy?' and it is a good question, because of course it's relevant, it's purely that at the time, as we're aware, there was a lot of data being published and shared in relation to vaccine efficacy globally, but there was a deficiency and inequality in the amount of safety data that was being shared and generated so that's why we focussed more on the safety aspect, rather than efficacy - just going through the questions - I mean [Vaccine Safety Lead, Sweden] raises a very good question, 'do countries feel that they have adequate support in the conduct of active vaccine safety surveillance studies?'. Again, a question to throw out to the floor, or to the ISoP committee, it would be fantastic to hear what people thought on that, do you feel you're getting enough support in, in the conduct of your safety studies, is there more work that can be done, and if you do need support what is that support you need?

Chair #2: So I would invite any, mainly folks in the, maybe pharmacovigilance in the country regulatory - in the NMRA, or in the EPI program or any now in relation to the vaccines or anybody who's working in pharmacovigilance even academia, who would like to chime in on [Vaccine Safety Lead, Sweden]'s question, that's fine.

Chair #1: [Chair #2], I think that the support for active pharmacovigilance safety surveillance studies is required because this is a process that is quite resource intensive. Some countries, I know, even in Uganda, some countries that are specifically studying safety, safety of vaccines in pregnancy, but I don't know whether this has been applicable to COVID-19, I've not heard about safety of COVID-19 vaccines in pregnancy, but what I believe, at least from the Ugandan perspective, yes, the support is there, [unintelligible] establishing the system, maybe - maybe even registries can be considered or, like harmonization, having harmonized surveillance systems that are regional, that can, that can quickly answer this because of the resource, resource requirements needed, but I think that, yes, to answer [Vaccine Safety Lead, Sweden]'s question, that adequate, that support is needed, I don't think it's adequate as yet, and as you see the priorities from [Researcher #1] study it is important both from the patient side, from all stakeholders, the whole post market surveillance, especially low and middle-income countries is an important issue, thank you.

Chair #2: Right Thank you [Chair #1] for that.

[Chair #3 resumed chairing of the discussion]

Chair #3: Alright. Thanks [Chair #1] for also answering, that I think if I can also comment to answer the question that was asked, is do we have sufficient support when it comes to the vaccine safety surveillance currently happening in the LMIC countries, I would like to say, yes, but there's still a lot of room for improvement, obviously, as [Chair #4] has said earlier, COVID-19 has brought a lot of, well good things in addition to not so good things, but some of the benefits that we can all appreciate is the fact that online has - online communication opened channels, especially between regulators and the rest of the stakeholders, including participants from the regulatory or, I mean participants from the manufacturing companies, as well as mainly people will support the pharma industry. What has been happening is, there's like like I say, there's a lot of room for improvement. There are countries that have really significantly improved in online communication, you know anytime there are issues and challenges towards a reporting of any safety issues whether COVID related or not, but we still do have countries where online communication has not been, optimised still to date, yeah? So we still do have countries where we are expected to report still manually or paper based and requiring physical submission in some in some oppor- in some countries, yeah? So those are the areas where I personally have had challenges and we would require to sort of start

having discussions around that area to sort of at least level the playing ground for all LMIC country so that if you're seeing online reporting, especially now during the COVID pandemic season, then that should be, I mean it should be a minimum requirement for everyone, you know and I think, as ISoP some of the collaborations we are looking towards is trying to have discussions around that area, looking for support framework that can be able to at least have a regulatory framework that can be able to support at minimum all the LMIC countries, at least to have a bare minimum. Yeah that's something I wanted to want to, especially from the pharma industry perspective. I'm also seeing a comment from-

Chair #4: Maybe just to add on that point that you have said, I think, yes, apart from just like the support that could be extended towards the LMIC, I think, also collaboration is key, because reinventing the wheel becomes kind of more expensive so for the countries that have done it and for the countries that are looking at doing it, so I think these conversations and just leveraging on the already available resources will also go a long way in strengthening the capacity, rather than everybody wanting to go alone to call it shorts and yeah so that's also one thing that can help in these collaborations and just strengthening their surveillance.

Chair #3: I like that.

Chair #4: Thank you.

Chair #3: I think just switching gears there is a comment that I've seen from both [Pharmacovigilance Specialist, Hospital, Kenya] as well as- oh, we have [Head of Pharmacovigilance and Clinical Trials, NMRA, Zimbabwe] on the mic, sorry sorry [Head of Pharmacovigilance and Clinical Trials, NMRA, Zimbabwe] please take over and ask your question I hadn't seen that.

Head of Pharmacovigilance and Clinical Trials, NMRA, Zimbabwe [Participant]: Hello good afternoon, Good morning, good evening, everyone can you hear me? OK, so I just have two comments I'm just responding to [Vaccine Safety Lead, Sweden] and [Vaccine Safety Expert, Switzerland] comments [in the chat], so [Vaccine Safety Lead, Sweden] was asking about active surveillance and whether there is adequate resources, so I was like Yes, they do need for more resources, because those projects are usually quite resource intensive and we are experiencing that in Zimbabwe, and we are currently conducting active AEFI surveillance, and then the second comment was from-

[Head of Pharmacovigilance and Clinical Trials, NMRA, Zimbabwe, loses connection]

Chair #3: But I think we can move on to maybe the last comment just give one last comment before we wind up the session and hand over to both [Researcher #1] and [Researcher #2] but there were two comments that I wanted to share or other one was a question that had been asked by [Research Officer, University, Nigeria], 'please, do you have information on the safety of COVID-19 on nursing mothers, especially on breastfeeding mothers?' that's a question that was asked, and then there was also a comment by both [Pharmacovigilance Specialist, Hospital, Kenya], 'we need support in terms of keeping up with new info, also healthcare workers, contributing to the real-world data. If more is reported and shared in terms of case studies, it will help in building knowledge. Then, those with the facilities can provide better patient information. There are fears among those with comorbidities pregnancies and they need to confidently be assured as our patients' and I totally agree with that and maybe [Researcher #1] and [Researcher #2] as I hand over to you, would you like to just give maybe one last word to [Research Officer, University, Nigeria] and [Pharmacovigilance Specialist, Hospital, Kenya]'s comments?

Researcher #1: Okay, no problem, I just have seen we've got another hand raised just before we, we move on, I will come back to [Pharmacovigilance Specialist, Hospital, Kenya] and [Research Officer, University, Nigeria]'s questions, but [Pharmacist, India], please do take the mic.

Chair #3: um I think we lost [Pharmacist, India]. All right, um.

Researcher #1: No problem happy to, to move on, there, and these are the joys of online workshops in this day and age. So yeah absolutely [Research Officer, university, Nigeria] off the top of my head and breastfeeding isn't my area of expertise, but again it's good to expand on these areas of women's health and safety in relation to the COVID-19 vaccine. Again it's something that some good to take in mind as we discuss this idea of forming working groups in the future and if we do create groups centred around pregnancy, maternal health, childcare, that is absolutely something that should be, it should be born in mind and, and represented in those working groups. I'm just looking for [Pharmacovigilance Specialist, Hospital, Kenya]'s comments.

Chair #3: Maybe I can read that for you again if you don't mind.

Researcher #1: Yeah absolutely go ahead.

Chair #3: So I [Pharmacovigilance Specialist, Hospital, Kenya] said 'we need support in keeping up with new information as healthcare workers, contributing in real-world data. If more is reported and shared case studies, it will help in building knowledge and, and those who are working at health facilities can be able to provide better patient information. There are fears amongst those with comorbidities, pregnancies and there needs to, we need to create complete confidence to assure our patients' so I guess that was just a comment and maybe I wanted to ask you more on that.

Research #1: Yeah fantastic comment and yeah thank you [Pharmacovigilance Specialist, Hospital, Kenya], really interesting to hear, and, and really interesting, as we saw in the results of the survey as well, but this, this aspect of the safety of administrative of the vaccines in co-morbidities is really something that we've seen interest in across the board. So really good to hear about the, the range of interest and the different conditions that we discussed today as well, but also interesting to hear about the, the communications aspect and I get- I guess, a lot of that comes down to awareness and educating when you talk about increasing reporting, but also the very important point you made earlier about ensuring that feedback is cascaded down to all levels of people engaged in pharmacovigilance and, and all levels of the healthcare system so yeah absolutely a really important point.

[At this point the poll was introduced by Researcher #1 and conducted within the webinar]

01:58:17

Chair #3: Thank you, thanks again for taking us through that. As we've come to the end of our webinar today, I would like to take this opportunity and really thank you, everyone who has been able to participate in today, to all the participants have taken the time from their day to day, their workplace and just their normal duties to just come and join us for these events we really, thank you for taking and, and for really taking the time to come and be with us. I also wanted to take this opportunity and thank all our chairs, our panellists today, our presenters, thanks again for taking us through the, you know the results of a – of a - of a survey that we were able to conduct about four months ago, and it really has been an eye opener just to see where we're at in terms of pharmacovigilance, the areas that it can be able to see me days, also with some of the collaborations that are highlighted earlier by [Chair #4] and we really have received a lot of comments, we received a lot of questions, some of them were answered some of them were not answered satisfactory, but I just want to assure everyone that all this data will be gathered together and they're going to be responded to in writing for anyone who feels that any of their comments questions were not satisfactory answers just know that we will get back to you on email and you'll be able to get your response, as was said earlier, the recordings of the sessions, along with the any other additional material that will be shared, there is a link that will be shared, where you'd be able to find all of these that will be posted I believe right now there is a link that is being shared on the chat box. Please distribute that before you log out just so that you can be able to you know get

access to all this material that is there. We would be grateful if you just complete the evaluation form if you've not if you were not able to get access to to eat earlier. It's it's also going to be shared on the chat box now, and also on email, please feel those and we'll be able to just help us be able to plan better for other events and also more. What what what really benefited everyone during today's webinar with that, I think, I would like to take this opportunity and thank everyone once again for all your participation, and I believe it's at this point that we are going to close off the seminar Thank you.

[End of workshop]

13 Workshop Q&A Questions and Comments

"*Are the UK's NHS's recruiting practices brain-draining poorer countries significantly -- of skilled staff who are badly needed at home?*" - **Research Professor in Neurosciences, Retired, US**

"Good evening the organizers. I am [personal details redacted]. I registered for the workshop and I am glad to attend to it. I would like to know the procedures of becoming a member of this Pharmacovigilance team." - **Biomedical Laboratory Technologist, University, Uganda**

"Great presentation and work on PV priorities. Do you think these priorities can be extended beyond the pandemic? I can see that they focus on safety mostly which is relevant across board?" **PhD Student, University, UK**

"Thanks for the great talk and insights. Regarding priorities and your comments on things yet to be determined - could you or members in the room comment on their experience with usability and or availability of tools available (eg, the Med Safety App or other you use in your countries), to support/advance work in the reporting and monitoring of adverse events associated with medicines and vaccines used during the pandemic? Thanks a lot." **Independent Consultant, Pharmacovigilance Consultancy, Germany**

"Does ISoP have any particular ongoing research on Covid-19 Vaccines in the West Africa region?" **Vaccine Security and Logistics Consultant, Human Resource Consultancy, Nigeria**

"Is there any website or reliable source of emerging (new) information where the safety of the COVID-19 vaccine can be sought be health professionals?" **Pharmacist, Regional Health Authority, Kenya**

"For being member of team, what is the requirement?" **Clinical Quality and Research Director, Medical Centre, DRC**

"Do you think the use of Real World Data (RWD) has a role to play in the COVID-19 vaccination safety monitoring/PV? And how?" - **Anonymous Attendee**

"I would like to know that why do you not include question regarding COVID -19 vaccine efficacy?" **Secretary and Researcher, Vaccine Research Organisation, India**

"Please have a look at this website https://covid19.ergonomics.org.uk/" **Managing Director, Pharmacovigilance Consultancy, UK**

"Does the Medical Safety App enter data points directly into a tracking database like ARGUS?" **Senior Pharmacovigilance Associate, Pharmacovigilance Consultancy, Australia**

"Please will like some of the tools web site be outlined for us to know them and used appropriately. Thanks" - **M&E Focal Person/Pharmacist, Regional Health Authority, Nigeria**

"Thanks a lot for the presentations. I wanted to ask whether some signals have been identified related to COVID vaccine safety monitoring by the different countries represented here?" **Research Officer, NMRA, Uganda**

"Hi everyone and thanks for the webinar, it's quite informative. Is it possible to revise the current AEFI reporting tools to be as comprehensive and capture the various age cohorts and populations as outlined by [the survey outcomes]?" - **Ministry of Health Official, Ministry of Health, Kenya**

"This is a contribution. The Africa collaboration was initially at the WHO-CC Accra until lately when the new initiative has come." - **Patient Safety Advocate, Advocacy Group, Zambia**

"I my country Zambia there are many self-serving entities on PV and a disconnect." **Patient Safety Advocate, Advocacy Group, Zambia**

"How is the collaboration with the Pharmacovigilance responsible in LMIC with developing country manufacturers? These companies are striving to mature their PV systems and implement best PV practices"
Vaccine Safety Expert, Research Facilitation/Funding Organisation & Vaccine Research Network, Switzerland

"Do countries feel that they have adequate support in the conduct of active vaccine safety surveillance studies?" - **Vaccine Safety Lead, Research Facilitation/Funding Organisation, Sweden**

"Thank you for your presentation! I think the current pandemic can be a huge opportunity to make healthcare professionals and general public aware of the various ADR reporting tools. This can be of benefit post pandemic as well." - **Lecturer and Researcher, University, Zimbabwe**

"Obtaining follow-up information could be a major challenge as instead of 2 follow-ups, only 1 follow-up is conducted currently as a result of the pandemic and busy HCPs may not have the time to respond to so many follow-ups especially in countries with large volumes of AEFI reports." **Country Safety Lead (Emerging Markets), Pharmaceutical Company, Nigeria**

"Thanks for the presentation. In Uganda, we have not conducted a Pharmacovigilance/safety research during the pandemic. Patients that get vaccinated are not given information about the vaccine." - **Biomedical Laboratory Technologist, University, Uganda**

"We are conducting active vaccine safety surveillance in Zimbabwe and yes such project require lots of resources but essential I think for evidence based PV." **Head of Pharmacovigilance and Clinical Trials, NMRA, Zimbabwe**

"As someone working in PV in industry - how would I be able to contribute to these programmes to assist in collecting data, or anything else that can contribute to better drug safety especially in the identified groups?" –**Director, Pharmacovigilance Consultancy**, **South Africa**

"While we are focused on Licensed Medicines' safety, should LMIC expand the remit of PV to consider unlicensed products (health supplements) or medicines used off label in the treatment of COVID illnesses (ie Ivermectin)?" - **Anonymous Attendee**

"Factually, people are being vaccinated without being tested for COVID infection first. It is very possible most people are either asymptomatic. Is there no cause for alarm, with respect to AEFIs?" **Anonymous Attendee**

14 Workshop Chat Box Comments

Comments received from workshop participants via the chat function which specifically related to pharmacovigilance in LRSs and this research project are presented below:

"*The Med Safety App by the FDA has been very instrumental to health workers and the general public in reporting of ADR's.*" - **Regulatory Officer, NMRA, Ghana**

"*I believe the key issue facing LMIC [sic] is safety communication. There is some lack of hesitance and confidence in communicating safety information, creating an environment of lack of trust between the ministries, regulators and the public has a ripple effect, vaccine hesitance, infodemics becomes unmanageable.*" - **Senior Program Officer, Intergovernmental Organisation, Uganda**

'*PV information does not reach the users of vaccines and more fear is raised when different vaccines are used for first jab and second or booster [sic]. This needs to be improved through the communication media'* - **Quality Assurance Advisor, Clinical Research Centre, US***

"*I think the topics presented are important and relevant. They can be applied in my region and at my place of work*." - **Professor, University, Brazil**

"*What is the relationship between COVID vaccine [and] diabetes?*" **Health Tutor/Lecturer, College, Ghana**

"*Do we have information on the safety of COVID-19 vaccine on nursing mothers, especially on breasting feeding?*" - **Research Officer, University, Nigeria**

'*These priorities are still relevant, however, the communication between the population and the national authorities need to be improved*' **National Director of Health Intelligence, Ministry of Public Health, Ecuador**

"*Do you have short professional courses for PV that young professionals can access?*" **Lead Pharmacist, Clinical Trial, Sierra Leone**

"*I think some priorities are overtaking some, as new vaccination guidelines emerge. For example, the approval of vaccination in children is now an emerging concern in my country. This is mostly because the general public were made aware just few months prior that children should not be vaccinated against COVID*" - **Lecturer and Researcher, University, Zimbabwe**

'*There is an inherent assumption that when we do PV, the information we get from the field reports are of good quality. This is not necessarily always the case. And as we collect poor data, we are unable to make good assessments or even provide the necessary feedback back into the field. I think PV in LMIC setting must consider this seriously - How must we improve data collection and also make it easy?*' - **Senior Fellow, University, Philippines**

"*How can further engagement be done on this discussion, very interesting one. How can I engage with my organization?*" - **Medical Laboratory Scientist, National Public health Institute, Nigeria**

* Note that this participant's location may have been obscured via the use of a VPN, see **VI32.1**.

15 Working Group Registration Form

Aims

1) To inform GPV members and workshop registrants of the workshop outcomes (PV priorities)
2) To invite GPV members and workshop registrants to join a working group(s)

Population of Interest

GPV members and 'What are the priorities for pharmacovigilance in LMICs during the COVID-19 Pandemic' workshop attendees.

Notes on Formatting in this Document

This survey consists mainly of 'tick box' type question responses. If this is not the case for a particular question, this will be identified in italics and square brackets, eg [*Free Text*], [*List*]

Questions that are optional are indicated in the same way, [*Optional*]. All questions are considered compulsory unless indicated otherwise. Dependent questions are also highlighted in this way, eg [*If answer to X was X*].

Page 1: Welcome!

Welcome! This is an invitation to join globalpharmacovigilance.org's (GPV) **Pharmacovigilance in Low and Middle-Income Countries during the COVID-19 Pandemic Working Groups.** This form has been developed following the recent GPV survey and GPV/ISoP Africa Chapter online workshop 'What are the Priorities for Pharmacovigilance in LMICs during the COVID-19 Pandemic?'.

Both the survey and the workshop aimed to agree consensus on the highest priorities for pharmacovigilance at this point in the COVID-19 Pandemic, where support, training and guidance are needed.

Global Pharmacovigilance now invites you to join a working group(s) to address the highest priorities identified following the survey and workshop. Following analysis of our results, we plan to create working groups to focus on the following areas:

- The safety of COVID-19 vaccination in pregnancy
- The safety of COVID-19 vaccination in children/adolescents
- Analysis of COVID-19 vaccine safety data

Whether you are an experienced pharmacovigilance professional, or simply someone with a passion for improving the safety and efficacy of medical interventions, we invite you to take an active role in guiding the activities and outcomes of these groups. Any number of approaches could be taken to address these challenges; this could include the development of training resources, the hosting of workshops/webinars, writing position papers, protocols or guidelines, but the exact outcomes will be determined by you as a group member. In addition, if you have experience working in any of the areas listed above, we invite you to take on a coordinating role in that working group. Working group activities will be supported by The Global Health Network, and the GPV platform will be used as a space for group activities and the dissemination of outputs.

This form consists of 8 questions and will take less than 5 minutes to complete.

Thank you in advance for your collaboration.

Please Note

The findings of this research may be published in a report, a scientific journal and/or presented at a conference. Your identity has been requested to allow follow-up contact only in relation to future working group activities and will remain anonymous in all publications and presentations of the findings.

The information that you supply will be treated in accordance with the University of Oxford's Data Protection policy. This project has been reviewed and approved by Oxford Tropical Research and Ethics Committee (OxTREC). Reference number OxTREC 541-18. For any other queries please email ryan.walker@ndm.ox.ac.uk

Page 2: Working Groups

Below are the themes of the three working groups we plan to create, to address the immediate need for support, training and guidance in these areas.

Note that completion of this form is an expression of interest, and does not place you under any obligation to be involved in future working group activities.

1. Please indicate which of the below working group(s) you are interested in joining. **You may select multiple groups**.

- WG 1: The safety of COVID-19 vaccination in pregnancy
- WG 2: The safety of COVID-19 vaccination in children/adolescents
- WG 3: Analysis of COVID-19 vaccine safety data

2. If you have experience in any of the areas these working groups seek to address, we invite you to take up a coordinating role within that group. **Are you interested in taking on a coordinating role within any of the working groups?** [*Optional]*

- Yes, I am interested in a coordinating role within one or more of the working groups
- No, I am not interested in a coordinating role within any of the working groups at this time

2.a *[If answer to Q.2 is yes]* Please select the working group(s) in which you are interested in taking a coordinating role:

- WG 1: The safety of COVID-19 vaccination in pregnancy
- WG 2: The safety of COVID-19 vaccination in children/adolescents
- WG 3: Analysis of COVID-19 vaccine safety data

Page 3: General Information

3. Which country do you work in? If you work in more than one country, **please select the country in which you work primarily.**

[UN Countries List, dropdown box]

4. Which of the following categories describes your current role? If you work in more than one capacity, **please select all that apply.**

- Nurse
- Doctor
- Pharmacist
- Medical Officer
- Pharmaceutical Technologist/Pharmacy Technician (Clinical)
- Pharmaceutical Technologist (Pharmaceutical Industry)
- Regulator
- Laboratory Scientist
- Pharmacovigilance Scientist
- Pharmacovigilance Officer
- Technical Advisor
- Qualified Person for Pharmacovigilance
- Analyst
- Consultant
- Academic/Researcher
- Student
- Other*
    - **If you selected Other, please specify:*

5. What type of establishment do you work for? **If you work for more than one establishment, please select all that apply.**

- Hospital (Public)
- Hospital (Private)
- Community Health Centre/Facility
- Private Practice or GP
- Community Pharmacy
- Non-pharmacy Drug Dispensing Outlet
- Ministry of Health
- Regional Healthcare Authority
- Regulatory Authority
- Government Research Organisation
- Public Health institute
- Immunisation Program
- Non-Government Organisation (NGO)
- Pharmaceutical Company
- Biotechnology Company
- Pharmaceutical Wholesaler
- Contract Research Organisation (CRO)

- Research Funding Organisation (RFO)
- Consultancy
- University/College
- Professional Society
- Journal
- Other*
    - **If you selected Other, please specify:*

6. For how long have you been involved in pharmacovigilance?
'Involvement' can include paid or pro bono work, consultancy, research, post-graduate study etc.

- Less than 1 year
- 1-5 years
- 6-10 years
- 11-20 years
- 20 + Years
- I have not had any involvement in pharmacovigilance up to this point

6.a. If you have not had any involvement in pharmacovigilance up to this point, please briefly describe your interest in joining this working group(s)

Kindly provide your contact details:

7. Name:

8. Email Address:

Page 4: Survey Complete

Your responses to this survey have been submitted.

If you need a formal record of your submission, please use the following details:

[Completion Receipt]

[Responses Download]

Thank you for completing this form. We will be in touch very soon to update you on the next steps for these working groups, and the first group meetings.

Thank you for your collaboration,

The Global Pharmacovigilance Team