TITLE PAGE: Justified emergency medicine research

Justified Emergency Medicine Research

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Abstract

My research uses the case of emergency medicine research to challenge established norms of governance and regulation which reflect an influential regulatory model of research ethics. This model has two foundational pillars: regulatory review and participant informed consent. Emergency research, where the possibility of consent is unclear, destabilises the pillar of consent and raises questions about the decision-making justification for emergency research. It asks how we may justifiably decide the research is permissible under a waiver of consent.

In **Chapter 1**, I outline the nature of the regulatory model of research ethics. I also offer key definitions and theoretical distinctions. These include the distinction between the ethics of research decision-making and the ethics of the research itself.

In **Chapters 2 and 3**, I characterise a landscape of issues relevant to the question of emergency research decision-making. For this I use case studies and regulatory responses arising in three research jurisdictions (the United States, the European Union and the United Kingdom). Having developed themes from case and regulatory analysis, I argue there are two main areas of decision-making to be justified: at the general level of regulatory review, and the individual level of each participant's enrolment.

In **Chapter 4**, I justify decision-making at the level of regulatory review, uniting my arguments with existing emergency research regulations. In particular, I examine whether the current formulation of the US regulatory requirement for prior consultation with communities about the research contributes to the justification. I argue that regulatory review is justified by reason of: securing commitment to emergency research under a consent waiver as a common purpose; judging the research's risks appropriately; and

considering the research's impact on social injustice through an altered form of community consultation.

In **Chapter 5**, I turn to the justification for decision-making at the level of participant enrolment despite the emergency context and the participant's likely mental incapacity. Here I carve out a key role for the physician-researcher. I argue she is uniquely positioned to make ethical decisions about whether or not to enrol the emergency patient. Her decision-making secures a modest level of respect for the patient as a person worthy of moral consideration despite his mental incapacity. Her role is sensitive to, and avoids provoking, a deep concern in research ethics. Namely the use of patients by researchers as merely a means to the ends of the research.

In **Chapter 6**, I describe a number of key findings arising from the justifications made, and some important policy implications. I also make recommendations for future work and scholarly thinking where regulatory models of research ethics are used.

Chapter 1: Introduction, definitions and distinctions

Introduction

Background to the doctoral research

Although its discoveries to date have been ground-breaking, and its improvements to care significant, emergency medicine research, or emergency research for short, presents challenges for research ethics governance and regulation. Crucially, the setting of the research is urgent and its participants are suffering from life-threatening conditions. This makes the possibility of prospective informed consent to the research highly unclear. Yet conducting research on enrolled participants is vital to improve the evidence base for future emergency care and medicine. This marks a dilemma for ethical decision-making, based on governance and regulatory norms such as consent, about how we justifiably decide the research may proceed. The proposal that we should routinely waive consent to emergency research amounts to a regulatory red line, and has resulted in emergency research being banned in the past. It motivates questions about whether routinely waiving consent to the research is justifiable, and whether existing governance and regulatory norms may accommodate this, or require revision.

This is the background stimulus for my doctoral research. In this research, I use emergency research to critique the adequacy of a model of research ethics which is based on these existing governance and regulatory norms, and which has influenced current thinking in research ethics. I examine how we may justifiably revise this regulatory model with implications for governance and regulation.

My research focuses on this particular regulatory model of research ethics because I aim to justify the *making of decisions* about the ethics of emergency research. This justification is separate from the justification, or ethics, of the research itself. The ethics of

emergency research characterises pertinent ethical issues in particular instances of the research. However, the ethics of emergency research decision-making involves justifying the processes, roles and operations which weigh the ethics of the research in each instance. This model thus suits analysis of the ethics of emergency research decision-making.

Significance of the problem

The challenges raised by emergency research decision-making are significant because they take issue with this regulatory model of research ethics, and its reliance on prospective written informed consent. Emergency research is not alone among research which raises these challenges, but its characteristics generate particular ethical issues, shaping the decision-making questions and problems which follow in particular and interesting ways.

For example, in incapacity and paediatric research, participant consent is not possible but there is time to seek proxy consent or opinion. Alternatively, in cluster randomized trials, individual participant consent is not feasible and is waived, but the research typically adds negligible or minimal research risk. In big data research, waivers may be justified by balancing feasibility against lack of necessity arguments – it is not feasible to obtain consent from thousands of data providers, but analysing the data may not require consent because its activities may not require participant permission. In contrast, emergency research requires the waiving of both participant and proxy consent in the majority of cases because of participant incapacity and lack of time to seek proxy consent. It is unable to minimize risks in all instances. It also would seem to require consent because its interventions upon participants with life-threatening medical conditions often include breaches of bodily integrity. These breaches constitute the kind of research activity which

would usually require participant permission. Its characteristics therefore pose similar issues which are not tractable using the current regulatory model, and so pose particular and interesting problems.

To illustrate the issues, consider for the example the 'Horizons AMI' trial, performed on heart attack patients between 2005-7 in eleven countries including the US and parts of Europe[1]. Patients who presented within twelve hours of symptom onset were randomized to different anti-clotting therapies, and all but two patients (out of n=3602) are said to have provided 'written informed consent' p2220. However, obtaining written consent here would probably have involved compromising the consent process, and validity of consent, owing to participant incapacity and the emergency context. Yet consent was still obtained. This illustrates: the influence of the regulatory model of research ethics on what is taken to be ethical decision-making; and the particular problems which emergency research poses to decision-making.

The question of justifying decision-making involves making and emphasizing certain theoretical distinctions, and maintaining those distinctions within the work of the thesis. Firstly, I distinguish between two main structural elements of the influential model of research ethics: 1) regulatory review of the research and; 2) informed consent to the research. Secondly, I distinguish between the ethics of emergency research and the ethics of its decision-making. Thirdly, I distinguish between what justifies the research and what legitimates the research, taking justification as a type of argument which defends reasons

[1] Stone, G. W., B. Witzenbichler, G. Guagliumi, J. Z. Peruga, B. R. Brodie, D. Dudek, R. Kornowski, F. Hartmann, B. J. Gersh, S. J. Pocock, G. Dangas, S. C. Wong, A. J. Kirtane, H. Parise and R. Mehran (2008). "Bivalirudin during Primary PCI in Acute Myocardial Infarction." New England Journal of Medicine 358(21): 2218-2230.

for decision-making in real-world practice but without requiring actual acceptance of those reasons. (For more on each of these distinctions, see the Distinctions section below in this chapter).

One of the important contributions that conceptual analysis can make to complex debates is through the introduction of careful, substantive distinctions of meaning. The strength of arguments depends on meanings and assumptions, oftentimes hidden in premises. Careful distinctions make clearer what is being claimed and argued. Recognising and maintaining distinctions aids clarity within my own analysis of this particularly complex area of research governance, research ethics, and decision-making, and supports the formation of arguments. It also helps to see the challenges raised by my research question in a novel and illuminating way. During the thesis, I shall point out places where thinking about implementation and justification of the research and its decision-making fails to take account of these distinctions. This is often the source of a lack of clarity about how to act, or what to value in decision-making, resulting in problematic regulations or guidance. In the thesis conclusions chapter, I shall return to these distinctions, illustrating their value to my analysis and arguments.

Research questions

The research questions my thesis seeks to answer are:

- Main question 1: What justifies research decision-making to permit emergency research?
- Sub question 1a: What comprises and justifies research decision-making at regulatory review?

- Sub question 1b: what comprises and justifies research decision-making at the point of enrolment where consent would usually be obtained? This is envisaging that the majority of participants will ultimately be enrolled under a waiver of consent to the research, i.e. without their written informed consent.
- Main question 2: Does the regulatory model of research ethics (based in governance and regulatory norms) accommodate a justification for emergency research decision-making with minor adjustments? Or does it require fundamental revision? For example, does it require that we rethink the structure of the model, how its structural components interact, and whether different deciders or decision-making processes are warranted (such as consultation with communities from which future emergency research participants will be drawn).
- Sub question 2: what changes to emergency research regulations and guidance follow from a minor or fundamental revision of the regulatory model?

In the chapter sections which follow, I give key definitions of the nature, context and stakeholders of emergency research. I also describe how I will use case studies and emergency research regulations. Finally, I give further details of the three theoretical distinctions described above, and my overall approach to analysis in the thesis.

Definitions

1. Emergency medicine

Historically emergency medicine arose in response to battlefield injuries and industrialisation. For example, the Vietnam and Korean Wars are said to have significantly

developed US physicians' skills in life-threatening trauma and orthopaedics cases[2]. Serious accidents resulting from industrialisation and mechanisation also wrought developments in emergency care in civilian settings[3]. Such care developments built upon the expertise of existing medical specialisms such as surgery, trauma, anaesthesiology, neurology, orthopaedics and cardiovascular medicine. But the distinctively urgent and life-threatening presentation of cases required a new category of care and medicine, addressing a diverse set of health care needs[4]. This category evolved over time, its conditions and techniques largely based on those existing specialisms, but combined with 'enhanced triage [and]… the provision of most acute assessment and intervention'[5]. Emergency medicine is practised in hospital departments of 'Casualty', 'A&E' or the 'Emergency Room'. It is also practised outside these departments in other parts of the hospital (e.g. trauma, surgery), and in other non-hospital settings, for example the pre-hospital setting of ambulances, or field settings. Field setting examples of disaster medicine and travel or 'wilderness'

[2] Kaneria, A. M. (2015). "The history and development of trauma and emergency care in England." Trauma 17(1): 52-57.

[3] Sakr, M. and J. Wardrope (2000). "Casualty, accident and emergency, or emergency medicine, the evolution." Journal of Accident & Emergency Medicine 17(5): 314-319.

[4] British Medical Association website. Emergency Medicine https://www.bma.org.uk/advice/career/studying-medicine/insiders-guide-to-medical-specialties/nhs-career-choices/emergency-medicine . Accessed 26 May 2019. 'Doctors working in emergency medicine (EM) (also known as Accident and Emergency medicine) respond to cases of major trauma, medical emergencies and large volumes of minor injuries and illness. In some respects, the EM specialist could be seen as the hospital equivalent of a primary care practitioner such as a GP. EM specialists handle new cases as they arrive in hospital and their decisions can have immediate impact on the management of an illness or injury. This impact frequently stems from the specialist's judgement of a patient's condition and state, and the ensuing referrals to medical colleagues for continuation of intensive treatment. The working environment for an EM specialist is often hectic and unpredictable. It is fast-paced, challenging and heavily multidisciplinary.'

[5] FitzGerald, G., C. Codd, P. Aitken and M. Sinnott (2012). "Queensland Emergency Medicine Research Foundation: Special report." Emergency Medicine Australasia 24(1): 37-42.

medicine fall under the category of special interests in emergency medicine, as do military and conflict medicine[6].

2. Emergency research and role of case studies in the thesis

In the thesis, a person who experiences a life-threatening medical condition which requires urgent treatment in a first-responder[7], pre-hospital or hospital setting is an emergency medicine patient. I take research conducted on patients suffering from emergency medicine conditions to define emergency (medicine) research. In Chapters 2 and 3, I choose emergency research case studies which satisfy this definition, where at least one of the index interventions has potential for direct participant benefit. In addition, I am focusing on research in a context which uses or gives rise to regulations, guidance or policy specific to emergency research.

I use a recent review of research falling under the US emergency research regulations from 1996-2016 to illustrate typical pathology in the case studies of interest[8]. The pathologies are listed in Table 1 reproduced below:

2.1. Table 1: Typical pathology in emergency research under US regulations from 1996-2016

	Completed Studies (n = 28)	Complete + Ongoing (n = 39)
Cardiac arrest	10 (36)	12 (31)
Hemorrhagic shock	6 (21)	8 (21)
Traumatic brain injury	5 (18)	7 (18)
Stroke	2 (7)	2 (5)
Agitation	2 (7)	4 (10)

[6] See Society for Academic Emergency Medicine Interest Groups section at https://www.saem.org/get-connected/interest-groups . Accessed 27 July 2017.
[7] This is included to incorporate cardiac pulmonary resuscitation (CPR) research studies where trained members of the public operate CPR devices.
[8] Klein, L., J. Moore and M. Biros (2018). "A 20-year Review: The Use of Exception From Informed Consent and Waiver of Informed Consent in Emergency Research." Acad Emerg Med 25(10): 1169-1177.

Airway	1 (4)	3 (8)
Status epilepticus	1 (4)	2 (5)
Acute coronary syndrome	1 (4)	1 (3)

Data are reported as n (%).

Cases I use in Chapters 2 and 3 function to raise issues about regulatory review and consent in the thesis. All explicitly or implicitly address the issue of obtaining or waiving written informed consent within the emergency setting. This is irrespective of whether regulations at the time permitted waivers of consent in emergency research. I use these cases to map a landscape of ethical considerations relevant to the decision-making question. In particular, I look within the cases for responses from governance and regulation to the challenges mounted by emergency research.

I do not use case studies which examine emergency research undertaken in constrained resource contexts (e.g. health care systems compromised by war or disaster). This is partly because there is substantial disaster ethics guidance in the literature[9]. It is also partly because other issues specific to war or disaster contexts may divert analysis from central decision-making questions. That said, the thesis aims to yield results about emergency research decision-making justification which are generalizable to both resource-adequate and resource-constrained emergency research contexts.

3. The role of emergency research regulations in the thesis

An integral part of my thesis examines how emergency research regulations were harnessed in response to issues raised by cases. These regulations thus provide a foil and response to the case studies described. They show how regulators and policy makers tried

[9] WHO (2015). Ethics in epidemics, emergencies and disasters: research, surveillance and patient care: training manual. https://www.who.int/ethics/publications/epidemics-emergencies-research/en/ p17-162. Accessed 29 April 2019.

to address the ethical issues raised. Because the case studies occur before, during and after the implementation of the regulations, I place description of the regulations (from US, EU and UK jurisdictions) in Chapter 2, before the final case study (which occurs in Chapter 3). This reflects where the regulations are responding to the issues raised, in particular those raised by landmark Cases 3 and 4 (PEG-SOD and TROICA) which directly prompt formation of the US and UK regulations. In Chapter 2, I also begin the process of mapping the decision-making landscape by identifying themes the regulations have in common, or which are specific to the US EFIC Regulations.

In Chapter 3, I develop these themes further by linking them to the issues the cases have raised. The themes are a comparative grouping of features which are common to some or all of the regulations described. Their construction does not follow a formal thematic analysis approach as one would find in qualitative research. Rather, it follows a conceptual analysis approach to identify ethically significant themes which will serve the overall argument of the thesis.

The theme development spanning Chapters 2 and 3 establishes a focus within the thesis on justifying decision-making based on the requirements of the US *Exception from the Requirement for Informed consent in Emergency Research (US EFIC)* [10]. Of the regulations examined, these regulations represent the more demanding justification challenge to address within the thesis. What makes these regulations more demanding is that they include extra requirements for disclosures and community consultation (Chapter

[10] U.S. Government Food and Drug Administration. Exception from informed consent requirements for emergency research, 21 C.F.R. § 50.24. Available from https://www.ecfr.gov/cgi-bin/ECFR?page=browse Accessed 26 May 2019

3: Themes 4 and 5) which present particular resource and implementation challenges. Such requirements have been criticised for discouraging research and being hard to implement[11,12].

There are three advantages to focusing on the US EFIC Regulations. Firstly, I address the more demanding challenge, and put forward the strongest justification for research decision-making. I can then apply this justification to the other, less-demanding regulations and consider whether they should be altered in response. Secondly, I improve the understanding of the ethical basis for the regulations and hence reduce concerns they are being improperly implemented. Thirdly, because the US EFIC Regulations regulate therapeutic research, the research is required to have the potential for direct participant benefit. This focuses analysis of decision-making on important, unanswered questions about how to decide acceptable research risks, a key concern of Chapter 4 (justifying emergency research decision-making at regulatory review). The therapeutic orientation of requirements within these regulations is also relevant to the arguments of Chapter 5, where I consider the dual role of the clinical researcher who also is a physician with clinical obligations to seek the best care for her patient (see the next section for discussion of this role).

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[11] Nichol, G., E. Huszti, J. Rokosh, A. Dumbrell, J. McGowan and L. Becker (2004). "Impact of informed consent requirements on cardiac arrest research in the United States: exception from consent or from research?" Resuscitation 62(1): 3-23.

[12] Salzman, J. G., R. J. Frascone, B. K. Godding, T. A. Provo and E. Gertner (2007). "Implementing emergency research requiring exception from informed consent, community consultation, and public disclosure." Annals of emergency medicine 50(4): 448-455

4. The researcher as physician-researcher in the thesis

Here I discuss how I conceptualise the emergency researcher who is responsible for enrolment in emergency research. This sets the stage for Chapter 5, which defends a significant role for the physician-researcher in the justification for decision-making.

I take the emergency researcher (or researchers) in the thesis to have a dual care-research responsibility with respect to patients who are eligible for enrolment[13,14]. By this I mean that the researcher is motivated to recruit patients to the research to resolve questions of treatment uncertainty and inform future treatment of patients. However, as a physician conducting research with therapeutic interventions, from a beneficence standpoint she also has a duty to pursue therapeutic benefit for individual patients. She is therefore obliged to weigh her dual care and research roles in decisions about enrolment to therapeutic research. In research where normal consent is possible, this would involve discussing the differences between research and clinical care with potential participants as part of the consent process. In emergency research this discussion is not possible, and the researcher needs to manage the duality of the role alone without the patient's involvement. Tensions arising from the dual role may occur within one individual (the physician-researcher, or the research nurse), or several individuals within a clinical research team[15]. In either scenario, the ultimate 'decision to enrol' typically falls to the responsible physician. It is also likely that a physician administers, or is responsible for

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[13] Brody, H. and F. G. Miller (2003). "The clinician-investigator: unavoidable but manageable tension." Kennedy Inst Ethics J 13(4): 329-346.

[14] King, N. M. P. and L. R. Churchill (2008). Clinical research and the physician–patient relationship: the dual roles of physician and researcher. The Cambridge Textbook of Bioethics. A. M. Viens and P. A. Singer. Cambridge, Cambridge University Press: 214-221.

[15] I am grateful to Dr Ethan Cowan, emergency physician at Mt Sinai, New York, US for the following anecdotal scenario: the research associate checks the eligible patient can be enrolled with the clinical lead. Together the associate and the lead comprise that research-care duality at work within more than one individual.

administration of, the index therapeutic procedures within the research protocol to interrupt the disease course, which may save life. For this reason, I refer to the responsible enroller as the physician-researcher, as she is ultimately responsible both for enrolment generally, and for crucial therapeutic benefit decisions from index therapeutic procedures within this. This does not mean that other clinicians within the care team, e.g. nurses or physiologists, do not conduct enrolment, or do not face similar challenges in managing their clinical and research duties towards the patient. Rather, the central claim is about the unique positionality and responsibility of the physician-researcher who takes on research in addition to existing clinical obligations.

Distinctions

5. Defining a regulatory model of research ethics

Here I define a model of research ethics based on norms which have been established by the development of research ethics governance, and research ethics regulation. This is not the only model or account which may be given of research ethics. Rather, it is a suitable model to reflect thinking in research ethics which is based on those norms, and which is influencing current governance and regulatory arrangements. The model therefore operates in the thesis to provide a starting point for analysis of research ethics decision-making, which is concerned with interpreting that normative basis and implementing those arrangements. It is a foil for analysis and development of a justification for decision-making where existing norms and arrangements are capable of revision.

The model I define here has a bipartite decision-making structure with two distinct pillars: 1) decision-making at prospective regulatory review followed by 2) decision-making at participant enrolment employing 'normal consent'. (I define both pillars below). With regard to how the two pillars relate, some suggest that valid consent relies on regulatory

review to impose certain restrictions or manage which choices can be made at the point of participant enrolment[16]. Others regard consent as a form of bottom-up governance, or 'intelligent governance' of the research. This is on the basis that research approved at regulatory review proceeds ethically in practice based on who decides to consent to it[17]. While not defining consent's role in exactly in these ways, I do take this model of research ethics to relate consent to the regulatory review which precedes it. This is because decision-making at prior review shapes the permissible scope of the research and so terms of consent, and may also require changes to consent documents. Consequently, prior review influences the decision-making at enrolment and the obtaining of normal consent which follows. I also take normal consent to have regulative (though not gubernatorial[18]) force, as well as an ethically-substantive role in respecting participant autonomy. I now examine the role of each structural pillar in more detail.

[16] Miller, F. G. and A. Wertheimer (2007). "Facing up to paternalism in research ethics." Hastings Cent Rep 37(3): 24-34. Authors argue that protocols are made 'consent-worthy' by prior regulatory review and approval.

[17] Capron, A. (2014). Subjects, Participants, and Partners: What Are the Implications for Research as the Role of Informed Consent Evolves? Basic Bioethics : Human Subjects Research Regulation : Perspectives on the Future. I. G. Cohen and H. F. Lynch. Cambridge, MA, USA, The MIT Press.

[18] By this I mean I do not take decisions by participants steer or govern the course of research in a deliberate sense, contributing purposefully to a governance aim.

5.1. Role of prospective regulatory review in this model

Regulatory review, implemented by responsible bodies, is a prominent feature of influential guidelines about research ethics governance, and research regulations[19,20,21]. I define responsible bodies as Institutional Review Boards (IRBs) or Research Ethics Committees (RECs) which are responsible for conducting regulatory review[22,23]. In the UK regulatory review came about to satisfy US funding requirements for ethical review, with formal establishment of a system of UK RECs in 1991[24,25]. Processes of regulatory review have been adopted by the majority of research-active regions in both the global north and south[26].

Processes of regulatory review hold research to procedural and substantive standards of research ethics, including in most cases the requirement for normal consent. Where appropriate, regulatory review may permit the research with a waiver or alteration of normal consent. Generally waivers are appropriate when obtaining consent might affect

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[19] World Medical Association WMA (2013). Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, 2013 revision, Helsinki. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ Paragraph 23 Research Ethics Committees. Accessed 26 May 2019

[20] CIOMS (2016). "Council for International Organizations of Medical Sciences. International Ethical Guidelines for Health-Related Research Involving Humans. Geneva, Switzerland: Council for International Organizations of Medical Sciences https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf. Guideline 23. Accessed 26 May 2019.

[21] US-DHHS (2018). "The Common Rule. Code of Federal Regulations Title 45 Public Welfare Department of Health and Human Services Part 46 Protection of Human Subjects. §46.109 IRB review of research. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html Accessed 26 May 2019

[22] US-DHHS The Common Rule *op. cit.*

[23] GAfREC (2011). "Governance arrangements for research ethics committees: a harmonised edition. Prepared by the UK Health Departments: Department of Health Research and Development Directorate (England) National Institute for Social Care and Health Research (NISCHR) (Wales) Chief Scientist Office Scotland) R&D Division, Public Health Agency (Northern Ireland).

[24] Hedgecoe, A. (2009). ""A form of practical machinery": the origins of Research Ethics Committees in the UK, 1967-1972." Med Hist 53(3): 331-350.

[25] UK Health Research Authority website https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/research-ethics-service/. Accessed 13 April 2019.

[26] Office for Human Research Protections. International Compilation of Human Research Standards. https://www.hhs.gov/ohrp/international/compilation-human-research-standards/index.html. Accessed 4 March 2019.

research data validity and quality, when there may be major practical problems with obtaining consent, or when consent may cause distress or confusion of research participants[27]. However, waivers are still generally exceptional and inconsistent with the bipartite structure of this model of research ethics. Given this, it is therefore clear to see why research which routinely waives consent mounts an ethical challenge to this model.

5.2. Role of normal consent in this model

The actions of physicians and medical researchers in Nazi Germany, who forced prisoners to undergo inhumane and often deadly experiments, resulted in a lasting focus on prospective written informed consent to any kind of research involving human subjects[28]. From the 1960s onwards, the US National Institute for Health and Food and Drug Administration made prospective informed consent mandatory for patients receiving experimental drugs[29]. The US National Research Act of 1974 maintained this approach and set up a *National Commission for the Protection of Human Subjects in Research*. This was in response to continuing exploitation of participants in research, including the Tuskegee syphilis experiments which began in 1932 and were exposed by the media in 1972[30]. Cases of abuse of research participants in the UK were also exposed by those such as Maurice Pappworth[31].

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[27] Rebers, S., N. K. Aaronson, F. E. van Leeuwen and M. K. Schmidt (2016). "Exceptions to the rule of informed consent for research with an intervention." BMC Med Ethics 17: 9.
[28] Annas, G. J. and M. A. Grodin, Eds. (1992). The Nazi doctors and the Nuremberg Code: human rights in human experimentation. New York, Oxford University Press.
[29] Annas, G., & Grodin, M. (1992*). op.cit*
[30] Jones JH. (2008). "The Tuskegee Syphilis Experiment," in Emanuel, E. J., R. A. Crouch, C. C. Grady, R. K. Lie, F. G. Miller and D. D. Wendler (2008). The Oxford Textbook of Clinical Research Ethics. Cary, UNITED STATES, Oxford University Press, Incorporated. p86-96.
[31] Pappworth, M. H. (1968). Human guinea pigs: experimentation on man, Beacon Press.

Influential research ethics guidelines including the Nuremberg Code, Declaration of Helsinki and the Belmont Report situated written informed consent prominently[32,33,34]. For example, the opening paragraph of the Nuremberg Code states that 'The voluntary consent of the human subject is absolutely essential.' Article 26 of the 2013 version of the Declaration of Helsinki states:

> After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

In this model of research ethics, I take consent to have a foundational status. Within this status, I take it to play both a regulative- and substantive-ethical role. By regulative-ethical, I mean consent is necessary for ethical regulation of research: it gives the participant the final say on whether research is acceptable, and holds researchers to written commitments laid out in informed consent documents, which have been pre-approved at regulatory review. It yields procedural value as part of ethical research decision-making. By substantive-ethical I mean a deeper substantive ethical role which secures respect for persons or their autonomy. Faden and Beauchamp describe this role in their conception of informed consent as:

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[32] Nuremberg Code. "Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949. Point 1. Available from https://history.nih.gov/research/downloads/nuremberg.pdf Accessed 26 May 2019

[33] World Medical Association WMA (2013). Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, 2013 revision, Helsinki. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ Articles 25-32 on Informed Consent. Accessed 26 May 2019

[34] United States. (1978). The Belmont report: Ethical principles and guidelines for the protection of human subjects of research. Bethesda, Md.: The Commission.

> an autonomous action by a subject or a patient that authorizes a professional either to involve the subject in research or to initiate a medical plan for the patient (or both). p278[35]

This yields substantive value as part of ethical research conduct. Together, both roles maintain the foundational status of consent. I refer to consent within this model of research ethics as the obtaining of 'normal consent' by following the steps in Figure 1 below:

5.2.1. Figure 1: normal consent

In obtaining normal consent, the researcher secures prospective 'autonomous authorisation' for participation. This allows things to happen to the participant which usually require her permission (e.g. breaching bodily integrity by taking a blood draw). Procedurally, this is secured by the following steps:

- The patient or representative reads written information prior to the research
- The patient or representative has sufficient opportunity to digest information, reflect and consult others including the research investigators
- Consent is documented by signing a written consent form. Either the participant himself can sign, or a proxy.

6. Distinguishing the ethics of research decision-making from the ethics of research

My research aims to answer the question of what justifies research decision-making to permit a given instance or instances of emergency research. This aim is different from justifying emergency research itself, although the two often overlap in the discourse about the ethics of emergency research. The differences are subtle, since identifying reasons for why the research is ethical is often the route taken in order to arrive at reasons for

[35] Faden, R. R., T. L. Beauchamp and N. M. P. King (1986). A history and theory of informed consent. New York, Oxford University Press.

emergency research decision-making. In the course of this route, the account of the ethics of research which is given may shape the decision-making questions which are to be addressed. For example, if the ethics of emergency research is taken to be an issue of what risks are socially acceptable, then decision-making involves deciding who or what process permissibly determines social acceptability of risk[36]. This example demonstrates the limitations of not drawing a distinction between ethics and ethics of decision-making: decision-making questions are premised on a particular account of the ethics of the research, and particular assumptions about what matters. This potentially limits the proper scope of arguments for ethical decision-making which follow.

In service of distinguishing the ethics of research and its decision-making, a content-process distinction is useful. Broadly speaking, the ethics of emergency research refers to the content of ethical issues arising in particular research instances ('what' reasons). Based on the ethics of research (of which several accounts may be given), analysis encounters questions about the ethics of research decision-making. This broadly refers to the ethics of processes, roles and operations during regulatory review (and elsewhere) which weigh the ethics of the research ('who, when, how' reasons).

Although this process-content distinction is a useful starting point for defining the ethics of decision-making, reasons for justified decision-making may have a mixture of procedural and substantive characteristics. For example, in Chapter 4 I propose a reason of reasonable risk for justifying decision-making at regulatory review (see Chapter 4,

[36] McRae, A. D. and C. Weijer (2002). "Lessons from everyday lives: a moral justification for acute care research." Crit Care Med 30(5): 1146-1151. Social acceptability of risk is a key part of their justification and their risk decision-making algorithm addresses this. See also Chapter 4, Section 3.4.

Section 5.2). This reason depends on satisfying procedural criteria for deciding how risks are reasonable, but also on substantiated evidence of a supportive scientific background as part of the process.

6.1. Those who conduct research decision-making

I take those who conduct research decision-making to reflect the broad structure of the model of research ethics which I have described above. They are 1) the ethics committee which conducts regulatory review, and 2) those responsible for acts of enrolment, such as the physician-researcher.

However, in addition to these decision-makers, I acknowledge that decision-makers at regulatory review also comprise policy makers and authors of guidance documents[37]. The Research Ethics Committee (REC) or Institutional Review Board (IRB) will also take advice from researchers or other experts, the clinical community, other regulatory bodies, or other bodies which are required to be convened such as the data monitoring committee and the community consultation. I also consider the physician-researcher to take subtle cues from the patient himself or any available proxies at enrolment, and to take advice from community consultations and professional team discussions.

In short I acknowledge that decision-making is more diverse and complex in nature than I am presenting. Nevertheless I have focused on regulatory review (plus community consultation), and the physician-researcher for clarity of approach and structure, and to focus on the roles I think are most significant for making the justification.

[37] Such as the FDA Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research. (April 2013 version). Available at: https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf Accessed 19 April 2019.

7. Distinguishing justification and legitimacy in the thesis

I am focusing on justification in the thesis. I define and use 'justification' in my research as a type of argument which defends sufficient and coherent reasons for non-ideal, real-world practice, but *without requiring* actual agreement or acceptance of those reasons. In contrast, I take a certain account of legitimacy to be about actual agreement or acceptance of those reasons. So for example, when reasons are offered for decision-making, this is a question about justification. When those reasons are actually accepted, then it is an account of their legitimacy. In the thesis, I develop a justificatory argument by establishing a set of reasons to defend decision-making in emergency research. I then examine what practical arrangements follow, or stand in need of refinement which reflect this justification.

Some have claimed that legitimacy is less demanding than justification, and more able to accommodate pluralist and realist turns in argument[38,39]. While acknowledging there are deep-seated differences in the literature about the nature of the two concepts, I claim that justification is more suited to my analytical approach (see Approach to analysis section below). This analyses and develops reasons for decision-making in emergency research at a theoretical and conceptual level, and so is not primarily concerned with agreement or acceptance of the reasons given.

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[38] Smith, M. J. and D. Weinstock (2019). "Political legitimacy and research ethics." Bioethics 33(3): 312-318. The authors say that legitimacy is realist and pluralist. They contrast this with the 'justificatory project', a 'fully justified set of moral principles', which, unlike legitimacy, does not allow for a pluralism of moral views and realism in analysing acceptance of authority.

[39] Buchanan, A. and R. O. Keohane (2006). "The Legitimacy of Global Governance Institutions." Ethics & International Affairs 20(4): 405-437. Buchanan and Keohane also see justification as requiring overly demanding moral standards, such as justice standards. They argue this fails to accommodate the reality that people across societies and nation-states are diverse in their moral standards, including justice.

An additional reason why I have not focused on legitimacy is that it is more associated with political theory, and acceptance of authority of responsible institutions. The thesis does include consideration of the authority or 'legitimacy' of certain significant role-holders, such as the ethics committee, since this is a relevant issue in the case study analysis (see Chapter 2). However, too much focus on this over-emphasizes the role of actual authority or the political capital of those role holders in justifying decision-making, rather than prior reasons why they should be authoritative in the decision-making.

An example of a justification type of argument comes from a recent paper I co-authored on justifying governance of social science research[40]. Our argument calls for a fair process for governing research which allows appropriate investigation of society's stake in social research. This is based on a model of fair process which maintains social accountability of research governance using four conditions: 1) publicity of governance decisions; 2) relevance of decisions; 3) revision and appeal of decisions; and 4) regulation of conditions 1)-3). The model might suggest that, for example, decisions should be regularly publicised in order for the justification to hold. Yet the justification does not depend on any of the conditions in the model being met. Rather it holds without requiring, for example, that decisions are made public, although were they to be publicised they should be acceptable to the public. The justificatory argument therefore holds without legitimation, which might call for regular public disclosures of decisions made.

However, certain elements of my justification of regulatory review in Chapter 4 and in concluding Chapter 6 are contingent on real-world contexts and facts. These elements

[40] Sheehan, M., M. Dunn and K. Sahan (2017). "In defence of governance: ethics review and social research." J Med Ethics. 1-7. I describe this argument more fully in Chapter 4, Section 3.5.

within the justification rely on (are legitimated by) practices and attitudes with respect to the decision-making involved. I refer to these elements as 'empirical components' of justification in the analysis of accounts.

By focusing on justification, I maintain clarity about my overall approach to analysis (see below), and the type of argument which I am pursuing. This type of argument prioritises examination of justificatory reasons and bases at the theoretical level, but as the work progresses includes empirical components. Such clarity is also useful in critiquing other accounts in Chapter 4 which also use justificatory accounts with empirical components, but may do so in ways which are unintended, or do not support the account overall (see Chapter 4, Section 3, Criticisms of accounts subsections).

8. Approach to analysis

The approach I take to analysis in the thesis is situated within theoretical and conceptual bioethics. It uses concepts and arguments from the theoretical bioethics literature, or derives concepts and arguments from the emergency medical research literature. The conceptual element of the approach considers the way in which concepts are related and the strength, validity, appropriateness and adequacy of the arguments involved. In doing this, my analysis makes claims about the general nature of meaning and reason with respect to core questions of justification in the thesis.

I took this approach for two reasons. Firstly, this approach is rare in the literature specific to emergency research ethics, which mostly focuses on practice or implementation, with little on examining underlying assumptions, principles or concepts. Secondly, it is a more suitable approach for addressing foundational questions about reasons underpinning established regulations and practices.

9. Literature searches

During my research, I periodically conducted reproducible literature searches in three main bibliographic databases. Firstly, I used *PubMed* [41]. This database proved comprehensive for searching the medical research literature, for example yielding much of Chapter 2's case study literature. It also helped to link research cases to the responses in the bioethics literature via initial searches or follow-on searches using its 'Similar Articles' side menu. Secondly, I used *Web of Science*, the set of databases owned by Thomson Reuters[42]. Within *Web of Science* I used two database functions: 1) limiting searches to the index 'Science Citation Index Expanded (SCI-EXPANDED) --1945-present'; and 2) filtering the results by 'Highly Cited in Field', and 'Hot Papers in Field' (these are highly cited but also recent papers, since mostly highly cited papers take several years to build up their numbers of citations). *Web of Science* was useful as a cross-check against *PubMed* searches. The two functions I used also kept my searches abreast of the most recently published literature. Thirdly, I used *Scopus*, the set of databases maintained by Elsevier[43]. Again I used its search results as a cross-check against other bibliographic databases. *Scopus* also includes the databases *Embase* and *PsychInfo*. *Embase* is a database of European journals and so functioned to retrieve literature and governance material relevant to the EU emergency research context. *PsychInfo* is produced by the American Psychological Association and so contains a wealth of behavioural and social science

[41] National Center for Biotechnology Information. PubMed database. Available at https://www.ncbi.nlm.nih.gov/pubmed/ Accessed 26 May 2019
[42] Thomson Reuters. Web of Science database https://clarivate.com/products/web-of-science/ Accessed 26 May 2019.
[43] Elsevier. Scopus database. https://www.scopus.com/ Accessed 26 May 2019.

literature[44]. This literature was relevant to analysing behavioural and empirical literature on the community consultation and public disclosure requirements of the US EFIC Regulations.

I also used web resources for literature searches. Firstly, I used the *Search Oxford Libraries Online* platform from University of Oxford[45]. This was a helpful reference point for research ethics handbooks, and books on ethical theory and political philosophy. Secondly, I used *Google Scholar* to access materials which were not available from University of Oxford's own physical or online resources[46]. Finally, I used scholarly online resources such as *The Stanford Encyclopaedia of Philosophy* to aid my understanding of core concepts in normative ethics and political philosophy[47].

9.1.Challenges within bibliographic database searches

It was challenging to design comprehensive search strings for capturing research approved under the emergency research regulations. This was because abstracts or keywords (which are the core target of database searches) rarely included details of consent or governance arrangements. Similarly, abstracts did not usually state the time within which emergency patients were recruited to the research, so indicating an 'emergency' or 'urgent' recruitment. Furthermore the language of time was hard to search for comprehensively, since authors were using both qualitative (e.g. 'acute' or 'urgent') or quantitative (e.g. '1-3 hours after stroke') time descriptors. To address these challenges,

[44] American Psychological Association. https://www.apa.org/pubs/databases/psycinfo Accessed 26 May 2019.
[45] Search Oxford Libraries Online (SOLO). http://solo.bodleian.ox.ac.uk/primo_library/libweb/action/search.do?vid=OXVU1. Accessed 27 April 2019.
[46] Google Scholar. https://scholar.google.co.uk/. Accessed 26 May 2019.
[47] The Stanford Encyclopedia of Philosophy. Principle editor: Edward N. Zalta. https://plato.stanford.edu/ . Accessed 27 April 2019.

my searches of the medical research literature specified the following medical pathologies of interest:

- MI, myocardial infarction, “acute myocardial infarction”, cardiac arrest, CPR, chest compression, cardiogenic shock, acute coronary syndrome(s), defibrillat*
- stroke, ischaemic stroke, ischaemic, ischemic,
- resuscitation, acute, severe
- head injury, “significant head injury”, trauma, head injur*, injury AND sever*, “coma score”, major trauma, trauma victim(s)
- exsanguination, haemorrhage, haemorrhagic shock, blood substitute, artificial blood
- severe hypoglycaemia, critically ill

In searches of the bioethics, ethics governance, and empirical or attitudinal literature, I specified the following emergency research regulation terms:

- consent waiver, consent exception, exception from informed consent, EFIC, delayed consent, deferred consent

For specific search strings, please see Appendix A.

10. Chapter conclusion

In the introduction to this chapter, I gave a background to my doctoral research, noting the significance of the problem of decision-making in emergency research. I then offered definitions and distinctions which constrain and orient the work of the thesis. Firstly, I defined emergency medicine and emergency research (ER), also defining its eligible participants. Secondly, I described the role of case studies and the emergency research regulations in the thesis. This demonstrated a focus on the US EFIC Regulations which

constitute the main justificatory challenge in the thesis. Thirdly, I established a regulatory model of research ethics, against which decision-making will be analysed. In doing this, I illustrated the role of prospective regulatory review and normal consent within this model. Both regulatory review and normal consent involve ethical decision-making. Fourthly, I clarified that the aim in the thesis is to justify emergency research decision-making, rather than justifying emergency research itself. Fifthly, I described the type of argument I shall focus on making in the thesis (justification), while also acknowledging that elements of this argument rely on real-world contexts and attitudes. Finally, I set out my approach to analysis and gave details of my literature searches.

Chapter 2: Mapping a decision-making landscape using emergency research cases and regulatory responses

1. Introduction

In this chapter I illustrate how scientific discoveries in emergency research (ER) in the 1980s-90s have advanced emergency medicine. Nevertheless, the research has raised significant challenges for a regulatory model of research ethics, in particular challenging its foundational pillar of normal consent. In this chapter I present ER case studies to illustrate issues which were raised prior to the introduction of regulations specific to ER. I then describe responses from incoming ER-specific regulations which waive or except consent. Together, I unite the issues raised by cases and regulations into themes which map a critical landscape relevant to justifying decision-making. This mapping uses descriptive comparison and conceptual analysis which spans this and the next chapter. In this chapter I firstly identify themes which are common to all of the regulations described. Secondly, I identify two further themes specific to the US EFIC Regulations, but which connect to issues raised in this chapter, and Chapter 3 (Case 5: Polyheme). For this reason they also merit being themes. In Chapter 3 itself I shall complete the mapping, using conceptual analysis to link Chapter 2 regulatory themes to the issues raised by case studies. This completes the full development of themes, and full characterisation of the decision-making landscape.

I structure this chapter and Chapter 3 as a dialogue between the cases themselves and the regulations which occurred in response. This means that spanning Chapters 2 to 3 the structure is as follows: 1) Case studies 1-4; 2) emergency research regulations; and 3) Case study 5 which occurred after the emergency research regulations were in force and so responds to their introduction.

2. Emergency research challenges a regulatory model of research ethics

Emergency research in the 1980s and 90s was making ground-breaking discoveries in the care of life-threatening conditions. The International Study of Infarct Survival (ISIS) trials, running from 1981-1992, aimed to clarify optimal clinical practice amid an increasingly complicated choice of treatment regimens for myocardial infarction or heart attack[48]. Discoveries included that the beta blocker atenolol offered better survival rates in the first twenty-four hours after a heart attack[49], that streptokinase and aspirin was better in combination than other administration combinations[50], and that there was no significant difference between older and newer clot-busting agent regimens, also applied in different combinations[51]. The National Institute of Neurological Disorders and Stroke (NINDS) study in 1995 showed that ischaemic stroke patients benefitted from treatment with recombinant tissue plasminogen activator (rTPA), a clot-busting agent, at 3 month measures. The rTPA agent was given 'within 3 hours of the onset of ischaemic stroke', and was beneficial despite some increased risk of bleeding into the brain. In such patients, significant incapacity because of the condition and the short 0-3 hour therapeutic window for experimental treatment would have prevented obtaining prospective informed consent, what I shall call 'normal consent' in the chapter[52]. These studies contributed to

[48] ISIS 1. (1986). "Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group." Lancet 2(8498): 57-66.
[49] ISIS 1. *op.cit.*
[50] ISIS 2. (1988). "Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group." Lancet 2(8607): 349-360.
[51] ISIS 3. (1992). "ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group." Lancet 339(8796): 753-770.
[52] See Chapter 1: Introductions for further details of this concept.

current guidelines that recommend a 'door to balloon' time (time to coronary intervention and drug administration) of up to 90 minutes after heart attack[53], and giving thrombolysis up to 4.5 hour window after onset of stroke symptoms[54].

More recent studies have sought to change the temporal environment of the emergency. For instance, the ongoing (as of April 2019) 'Emergency Preservation and Resuscitation (EPR) for Cardiac Arrest From Trauma (EPR-CAT) trial' proposes a technique of suspended animation to halt catastrophic injury to trauma patients suffering from severe exsanguination (commonly known as 'bleeding out') [55, 56,57]. Its interventions – given to those already classed as 'clinically dead' – replace whole body blood with cooled saline and result in 'complete cessation of heart and brain activity'[58]. This buys up to one hour's extra time for surgeons to repair complex injuries before brain injury starts to occur. The body is then warmed back up to normal temperatures.

The examples show how emergency research has illuminated the pathology of emergency disease and advanced the practice of emergency medicine. However, they also show the dilemmas that emergency medicine poses for a regulatory model of research

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[53] Bradley, E. H., J. Herrin, Y. Wang, B. A. Barton, T. R. Webster, J. A. Mattera, S. A. Roumanis, J. P. Curtis, B. K. Nallamothu, D. J. Magid, R. L. McNamara, J. Parkosewich, J. M. Loeb and H. M. Krumholz (2006). "Strategies for reducing the door-to-balloon time in acute myocardial infarction." N Engl J Med 355(22): 2308-2320.
[54] Robinson, T., Z. Zaheer and A. K. Mistri (2011). "Thrombolysis in acute ischaemic stroke: an update." Ther Adv Chronic Dis 2(2): 119-131.
[55] ClinicalTrials.gov website. Trial record NCT01042015, Emergency Preservation and Resuscitation (EPR) for Cardiac Arrest From Trauma (EPR-CAT) https://clinicaltrials.gov/ct2/show/NCT01042015?term=NCT01042015&rank=1. Accessed 19 April 2019
[56] Tisherman, S. A., H. B. Alam, P. M. Rhee, T. M. Scalea, T. Drabek, R. M. Forsythe and P. M. Kochanek (2017). "Development of the emergency preservation and resuscitation for cardiac arrest from trauma clinical trial." J Trauma Acute Care Surg 83(5): 803-809.
[57] Bellamy, R., P. Safar, S. A. Tisherman, R. Basford, S. P. Bruttig, A. Capone, M. A. Dubick, L. Ernster, B. G. Hattler, Jr., P. Hochachka, M. Klain, P. M. Kochanek, W. A. Kofke, J. R. Lancaster, F. X. McGowan, Jr., P. R. Oeltgen, J. W. Severinghaus, M. J. Taylor and H. Zar (1996). "Suspended animation for delayed resuscitation." Crit Care Med 24(2 Suppl): S24-47.
[58] Squiers, W (2014)."Emergency preservation and resuscitation: a Lazarus trial?" The Lancet 384(9947): 939.

ethics which incorporates the requirement for normal consent (see also Introductions Chapter, Section 5.2). Emergency medicine lends itself to urgent intervention, or to intervention which interrupts the progression of disease pathology[59,60]. Research design must either streamline the time to therapeutic interventions, or artificially extend the therapeutic window. Both types of design create consent and governance issues, one reducing time to decide about the research further, the other prolonging patient mental incapacity (by interruptive interventions e.g. therapeutic hypothermia, which render patients unconscious or otherwise incapable). This means that usually neither patient nor their proxies have sufficient mental capacity to make decisions about the research. Furthermore, taking time to attempt consent may introduce unacceptable delay to treatment[61]. Overall the nature of emergency medicine, and its influence on research design and objectives, is not conducive to a regulatory model of research ethics.

3. Role of cases and emergency research regulations in this chapter and Chapter 3

As mentioned above, case studies in this section and Chapter 3 operate in dialogue with the description of emergency research regulations. Cases illustrate ethical issues relevant

[59]Muizelaar, J. P., A. Marmarou, H. F. Young, S. C. Choi, A. Wolf, R. L. Schneider and H. A. Kontos (1993). "Improving the outcome of severe head injury with the oxygen radical scavenger polyethylene glycol-conjugated superoxide dismutase: a phase II trial." J Neurosurg 78(3): 375-382. p376 'Even though the design of the trial allowed for the study drug to be administered within 12 hours after injury, it was considered best administered as soon as possible.'

[60]See also FDA Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research. (April 2013 version). Available at: https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf: p15 '43. *Must attempts to contact a subject's legally authorized representative or family member exhaust the entire therapeutic window before the test article may be administered to the subject?* No. FDA does not expect attempts to contact a legally authorized representative (LAR) or a family member to exhaust the entire therapeutic window before the test article may be administered. It would ordinarily be expected that the potential benefit of the test article will decrease as the delay in administering the test article increases…' Accessed 19 April 2019.

[61]Roberts, I., D. Prieto-Merino, H. Shakur, I. Chalmers and J. Nicholl (2011). "Effect of consent rituals on mortality in emergency care research." Lancet 377(9771): 1071-1072.

to the research. Regulations provide a foil and response to those cases. They show how regulators and policy makers tried to address the issues raised. Landmark Cases 3 and 4 (PEG-SOD and TROICA) are the most direct example of this dialogue, since they directly prompt formation of the US and UK regulations (see Section 4). In this section I present the cases, and in Section 4 the regulations.

3.1. Case 1: NINDS: context thwarts normal consent

The first case study is the *National Institute of Neurological Disorders and Stroke (NINDS) study* reported in 1995[62]. At the time the research was conducted, normal consent[63] was a requirement in ethics approval of emergency research[64]. The emergency research waiver of consent did not yet exist in research regulations. The case is important as it is one of very few cases in the literature from the pre-waiver era of emergency research regulation which makes an explicit, published claim about having obtained normal consent in the emergency research context. NINDS demonstrates how normal consent cannot do the required ethical work in emergency research. It points to the foundational status of consent in research ethics which is challenged by the reality of consent in the emergency research context. It also shows how consent has come to play both a regulative- and substantive-ethical role. It raises questions about whether and how to fulfil these roles in emergency research.

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[62] NINDS (1995). National Institute of Neurological Disorders and Stroke (NINDS) Study Group. "Tissue plasminogen activator for acute ischemic stroke." N Engl J Med 333(24): 1581-1587.
[63] See Chapter 1, Section 5.2 for the definition of normal consent.
[64] I take the process of normal consent to be both the regulatory norm at the time, and the research-ethics norm for obtaining a patient's autonomous authorisation for research to happen to him. This is to say I am assuming normal consent would have secured his consent appropriately and was 'valid' in this respect.

Stroke is defined as 'an acute neurological deficit lasting more than 24 hours and caused by cerebrovascular aetiology' of which ischaemic stroke is 'caused by vascular occlusion or stenosis' (blocked or narrowed arteries supplying blood to the brain)[65]. The NINDS study recruited ischaemic stroke patients to treatment with recombinant tissue plasminogen activator (rTPA), a clot-busting agent. The rTPA agent was given 'within 3 hours of the onset of ischaemic stroke', and was beneficial despite some increased risk of bleeding into the brain. Significant patient incapacity due to the stroke and the short 0-3 hours therapeutic window for experimental treatment would seem clear. This would have prevented patients engaging at all with the research, and certainly prevented normal consent from being obtained. Therefore, it is surprising to find claims in the trial literature that normal consent was obtained 'for all patients'[66]. Perhaps researchers were obliged to report they obtained consent when they did not, as part of regulatory approvals or publishing conventions at the time. Or perhaps they thought they obtained consent satisfactorily in the emergency context. The published claim which NINDS researchers make about consent raises a number of ethical issues. Firstly, it is unclear whether obtaining normal consent from patients or proxies is possible in context. From the clinical profile of patients, and characterisation of emergency disease in Section 2, this seems to be unlikely. Secondly, it is unclear whether consent should be attempted, if the likelihood is that neither patients nor proxies will have sufficient mental capacity. As a contributory factor, it seems the environment in which to promote mental capacity is not ideal: patients must be treated urgently, requiring urgent decisions from them or their proxies; patients

[65] BMJ Best Practice website. Ischaemic Stroke. http://bestpractice.bmj.com/topics/en-gb/1078. Accessed 19 April 2019.
[66] NINDS (1995) *op. cit.* p1582

and proxies are undergoing physical and mental strains. This second issue will be important when considering the value of individual participant assessment, since a context in which the possibility of consent is unclear may also discourage other participant-specific decision-making at enrolment (see Chapter 5 for the value of participant-specific decision-making). Thirdly, it is unclear what is achieved by attempting to obtain consent given the context. In the regulatory model of research ethics, consent has both a regulative- and substantive-ethical role, with different but interrelated functions[67]. On one hand, it functions as a necessity in research ethics regulation: it records participant agreement to the research, and commits researchers to the terms of consent documents[68]. On the other hand, it functions to confer the deeper, substantive-ethical values of respect for persons or their autonomy, and protection of the individual participant's welfare. These values constitute the autonomous authorisation which makes participant agreement valid[69]. Given the context of NINDS, it is likely that consent only performed its regulative-ethical role and function. In claiming normal consent was obtained, neither researchers nor IRB acknowledged that consent would have achieved little of ethical substance in the emergency context. It may even have risked more harm to patient welfare than good, given the urgency of the situation[70].

[67] See also Chapter 1, Section 5.2, Role of normal consent.
[68] Capron, A. (2014). Subjects, Participants, and Partners: What Are the Implications for Research as the Role of Informed Consent Evolves? Basic Bioethics : Human Subjects Research Regulation : Perspectives on the Future. I. G. Cohen and H. F. Lynch. Cambridge, MA, USA, The MIT Press.
[69] Faden, R. R., T. L. Beauchamp and N. M. P. King (1986). A history and theory of informed consent. New York, Oxford University Press. p277-8
[70] Roberts, I., D. Prieto-Merino, H. Shakur, I. Chalmers and J. Nicholl (2011). "Effect of consent rituals on mortality in emergency care research." Lancet 377(9771): 1071-1072.

In Case 1, I have shown the limitations of the role and function of normal consent in emergency research. Given the context, consent may only have performed a regulative-ethical role. Its use here may indicate a conflation of its regulative- and substantive-ethical roles, either unintentionally, or as a necessary equivocation by researchers or regulators. This speaks to an idealism around the concept of normal consent and the ethical value which it is capable of conferring, which did not account for the realities of the emergency research context. The final issue this case raises is whether the research is impermissible if consent cannot function to confer deeper, substantive-ethical values. This last issue is dealt with in more detail below (see Case 3: PEG-SOD).

3.2. Case 2: ISIS trials: simplifying research design impacts the ethical significance of enrolment

The second case study is also emergency research (ER) which occurred prior to incoming ER regulations. The case is a programme of research called the *International Study of Infarct Survival (ISIS)* for treatment of myocardial infarction (MI) or heart attack, using randomised placebo-controlled designs and comparisons of several standard treatments (beta-blockers, clot-busting drugs, aspirin)[71, 72, 73]. It contains no explicit statements about consent[74]. However, it is important in showing how simplifying the research's design has an impact on the ethical significance of enrolment procedures such

[71] ISIS 1. (1986). "Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group." Lancet 2(8498): 57-66.
[72] ISIS 2. (1988). "Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group." Lancet 2(8607): 349-360.
[73] ISIS 3. (1992). "ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group." Lancet 339(8796): 753-770.
[74] ISIS 1 (1986) *op.cit.* contains a statement in its acknowledgements 'to the thousands of patients who agreed to participate' but the meaning of 'agreed' is under-determined as it relates to normal consent.

as normal consent. Whether considerations of research design should influence enrolment procedures in this way is a relevant issue. Who decides whether enrolment is ethical when it deviates from normal consent is also a relevant issue.

The published literature describes how a 'simple' approach to design yielded large sample sizes for ISIS. For example, ISIS-1 was described as using 'very simple entry criteria, entry procedures, treatments, and follow-up'. In order '[t]o simplify, and hence maximise, patient entry, there was no entry form'[75]. This shows eligibility procedures were brief, documentation was minimised and inclusion-exclusion criteria were broad. This simple patient eligibility and entry approach allowed recruitment of multiple centres (245 centres in 14 countries) containing tens of thousands of cardiac patients (n=16027 in ISIS-1, n=17187 in ISIS-2, and n=41299 in ISIS-3 were reported). It suggests the research's design was simple because it altered or omitted normal consent.

This 'simple' design described in ISIS is similar to research design concepts which have argued for changes to standard regulatory procedures, including normal consent. One such concept is the 'pragmatic trial'. This tailors therapeutic research protocols so that the results are relevant to real-world settings[76]. ISIS-1 has been referred to as a pragmatic trial in the literature, namely a 'large, simple' trial which can control for sample bias because of the large, diverse randomized sample[77]. Another such research design concept is the 'learning healthcare system', which argues for research of increased design simplicity and

[75] ISIS 1 (1986) *op.cit* pg 58
[76] Loudon, K., S. Treweek, F. Sullivan, P. Donnan, K. E. Thorpe and M. Zwarenstein (2015). "The PRECIS-2 tool: designing trials that are fit for purpose." BMJ 350: h2147.
[77] Peto, R., R. Collins and R. Gray (1995). "Large-scale randomized evidence: large, simple trials and overviews of trials." Journal of clinical epidemiology 48(1): 23-40.

sample size to achieve seamless integration into clinical care provision[78,79]. Both design concepts argue for changes to normal consent paradigms as part of simplifying the design[80,81,82]. Justifying simple design thus seems to require altering or omitting consent. Two issues arise in emergency research from an approach to enrolment which alters consent based on simplified research design.

Firstly, simplifying design can result in a reductionist interpretation of consent. Authors of the learning healthcare system argue that because their proposed research studies are close to clinical care they assure basic patient welfare. On this claim, the authors imply that securing welfare is sufficient for ethical patient treatment at enrolment. As a result, studies are 'presumptively respectful of patients' rights and dignity' and so normal consent may be altered[83]. Critics counter that this interpretation of consent is reductionist since it 'bypass[es] a person's agency', even if basic welfare is secured[84]. In emergency research, patients are likely to lack agency since they lack mental capacity. Even so it still seems inappropriate to bypass the individual patient on such a reductionist interpretation of consent. The patient's incapacity may even exacerbate the issue of design being used as a reason to alter consent. This is because we seem to owe extra care or consideration

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[78] Roehr, B. (2013). "The appeal of large simple trials." BMJ : British Medical Journal 346.
[79] Faden, R. R., T. L. Beauchamp and N. E. Kass (2014). "Informed consent, comparative effectiveness, and learning health care." N Engl J Med 370(8): 766-768.
[80] Kim, S. Y. and F. G. Miller (2014). "Informed consent for pragmatic trials--the integrated consent model." N Engl J Med 370(8): 769-772.
[81] Faden et al. (2014) *op. cit.*
[82] Goldstein, C. E., C. Weijer, J. C. Brehaut, D. A. Fergusson, J. M. Grimshaw, A. R. Horn and M. Taljaard (2018). "Ethical issues in pragmatic randomized controlled trials: a review of the recent literature identifies gaps in ethical argumentation." BMC Medical Ethics 19: 14. https://doi.org/10.1186/s12910-018-0253-x
[83] Kim and Miller (2014) *op.cit.* Quoting: Faden R, Kass N, Whicher D, Stewart W, Tunis S. Ethics and informed consent for comparative effectiveness research with prospective electronic clinical data. Med Care 2013;51:Suppl 3:S53-S57.
[84] Kim and Miller (2014) *op.cit.*

towards the incapacitated patient in an emergency, as opposed to the lesser consideration which a simple design implies. (Although this is not to say that normal consent reflects extra care or consideration which is appropriate to the emergency context). Similarly, the concern in the ISIS case is that the emergency patient population exacerbates the ethical issues of simplified design, resulting in a reductionist interpretation of, and approach to, consent. This may be inferred from a passage on enrolment from ISIS-3:

> To encourage recruitment, the trial procedures were simple. Patient entry involved no forms (only a short telephone call to a 24 hr randomisation service)[85].

'Encouragement' might refer to encouraging *centres* to conduct enrolment or *participants* to enrol. The former meaning of encouragement suggests a simple design encouraged more centres to join the study and hit their recruitment targets. Such a design might well have reduced staff administrative burden, and increased emergency participant safety at enrolment[86,87]. The latter meaning of encouraging participants to enrol is more ethically complex: it suggests that normal consent in emergency research discourages (conscious[88]) patient or proxy engagement with the research, or results in hesitation from researchers themselves to enrol participants. While a written consent form may indeed be off-putting and insensitive in context, it seems too quick a move to suggest we abandon consent as a concept altogether. This risks missing the ethical significance of the enrolment encounter.

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[85] ISIS 3 (1992) *op.cit.*
[86] Roberts, I., D. Prieto-Merino, H. Shakur, I. Chalmers and J. Nicholl (2011). "Effect of consent rituals on mortality in emergency care research." Lancet 377(9771): 1071-1072.
[87] Harston, G. W., M. Sheehan and J. Kennedy (2014). "Emergency medicine research: rites, rituals and consent." Emerg Med J 31(2): 90-91.
[88] In some ER cohorts, participants are conscious at enrolment, and may be able to give some form of consent or assent to the research. See Sahan, K. M., K. M. Channon, R. P. Choudhury, R. K. Kharbanda, R. Lee and M. Sheehan (2016). "Refining the Enrolment Process in Emergency Medicine Research." Eur J Cardiovasc Med 4(1): 506-510.

A second related issue arising from altering consent based on a simplified research design is the assumption that different enrolment processes play similar ethical decision-making roles. This refers to the way in which the ISIS literature describes simple 'entry criteria, entry procedures', and 'patient entry…form'[89]. Entry criteria appears to be a reference to eligibility checks. Eligibility checks are a simple, technical review of the patient's medical history against research's inclusion-exclusion criteria[90]. Conversely, entry procedures and the patient entry form appear to refer to consent and written forms used in consent. These signify the enrolment encounter, entailing ethical decision-making. Negotiating entry, especially in context, is more ethically complex than checking eligibility. So by treating entry like eligibility, the ethical significance of enrolment is lost, and it becomes just another study protocol procedure. A further ramification of this is that researchers who conduct enrolment are no longer encouraged to see it as an ethically complex endeavour, and as such motivated by consideration of individual patients.

This last point raises issues about who or what process decided that altering or omitting consent was acceptable, and who took responsibility for the enrolment which followed. The implication is that having reduced consent's significance, ethical responsibility for enrolment moves away from the enrolment encounter. Instead it becomes housed within decision-making conducted at regulatory review. Regulatory review is then responsible for future enrolment, perhaps having approved an enrolment process for the researcher to follow. However, this asks the researcher to ignore an 'unavoidable but manageable tension' inherent in the practice of therapeutic clinical research. This is her conflicting

[89] ISIS 1 (1986) *op.cit* pg 58
[90] Though of course 'patient consents to the study' is also part of some eligibility checks

obligation as a physician-researcher, aiming both to benefit patients clinically and also to pursue scientific goals[91,92]. It is likely that such obligations and the instinct to be responsible persist in the physician-researcher, irrespective of how the research is designed, or what approved processes she might follow. In which case, she is unable to fulfil her responsibilities and ethical intuitions towards the patient.

The ISIS case has revealed that simplified research design is particularly problematic in the context of emergency research. The ethical significance of enrolment is suppressed in the name of simplified research design, when we should give it particular attention. Simplified design may also undermine the intuitions and responsibilities of the physician-researcher with dual clinical-research obligations towards her patient. Neither does it seem appropriate for regulatory review to take on full responsibility for ethical enrolment from researchers.

3.3. Case 3: PEG-SOD: altering normal consent in the US context

The 3rd case I use raises questions about the permissibility of altering normal consent to emergency research by discretionary IRB judgements without consulting certain other parts of the research establishment[93]. This is a landmark case which led to the development of the US EFIC Regulations[94]. The case is also notable for engaging extensively with issues

[91] Miller, P. B. and C. Weijer (2006). "Trust based obligations of the state and physician-researchers to patient-subjects." J Med Ethics 32(9): 542-547.
[92] Brody, H. and F. G. Miller (2003). "The clinician-investigator: unavoidable but manageable tension." Kennedy Inst Ethics J 13(4): 329-346.
[93] By 'research establishment' I mean those with professional stakes in the research such as researchers, IRBs, Sponsors, commercial partners, or consultants such as lawyers.
[94] U.S. Government Food and Drug Administration. Exception from informed consent requirements for emergency research, 21 C.F.R. § 50.24. Available from https://www.ecfr.gov/cgi-bin/ECFR?page=browse Accessed 26 May 2019

of consent and ethics regulation in the ethics literature. The case in question is PEG-SOD, which refers to two studies of polyethylene glycol conjugated superoxide dismutase (PEG-SOD) for severe head Injury. PEG-SOD was thought to limit brain damage by protecting cells from an oxygen radical, the superoxide anion.

Both studies engaged with and were responsive to ethical issues around normal consent. The first study was run by Muizelaar et al. in hospital sites in Virginia and Maryland, US[95], and the second run by Prentice et al. from University of Nebraska, US[96]. The first study used deferred consent with data withdrawal as an approach to enrolment. Researchers used deferred consent in order to administer PEG-SOD as soon as possible, delaying consent (with a temporal meaning of defer as 'delay') until after its administration. If subsequent objections were received, investigators withdrew data from the analysis for efficacy, (but not for safety)[97]. This approach seems inadequate, since it neither offers adequate respect (by not acknowledging consent cannot be deferred and so has not been prospectively obtained), nor advance the research's scientific aims (by limiting the knowledge that may be drawn from the data). Nevertheless, in this case researchers and the IRB engaged directly with the difficulties of consent in the emergency context, and were at least responsive to those difficulties in trying to make more appropriate arrangements. They were aware of, and felt accountable for, the issues involved in a way not seen in the previous two cases (Cases 1 and 2 above).

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[95] Muizelaar, J. P., A. Marmarou, H. F. Young, S. C. Choi, A. Wolf, R. L. Schneider and H. A. Kontos (1993). "Improving the outcome of severe head injury with the oxygen radical scavenger polyethylene glycol-conjugated superoxide dismutase: a phase II trial." J Neurosurg 78(3): 375-382

[96] Prentice, E. D., D. L. Antonson, L. G. Leibrock, V. C. Prabhu, T. K. Kelso and T. D. Sears (1994). "An update on the PEG-SOD study involving incompetent subjects: FDA permits an exception to informed consent requirements." Irb 16(1-2): 16-18.

[97] Muizelaar et al. (1993) *op. cit.* p376.

Investigators in the second PEG-SOD study (Prentice et al.), and the Nebraska IRB which approved the study, also engaged directly with the ethical issues involved. Writing in the journal *IRB*, the investigators specifically tackled ethical enrolment, proposing to adopt 'prospective proxy consent' where time allowed (though again the study drug was to be given as soon as possible)[98]. (This prefigured proxy consent arrangements in the incoming emergency research EFIC Regulations, see Section 4 below for details). However, the issue of enrolment without prospective consent was more complex. The study could not satisfy both trial-specific and general human research regulations, issued by the US Food and Drug Administration (FDA) and Department for Health and Human Services (DHHS) respectively. Therefore the IRB conducted its own ethical analysis and took legal counsel in order to make a discretionary judgement about the research. The IRB recognised the ambiguities in the term 'deferred consent' which had already been subject to criticism by others[99,100]. Nevertheless, their own analysis prompted local approval of an enrolment approach of no prospective consent with proxy consent after the emergency phase. This was 'deferred consent' in all but name:

> …the board decided to ask the investigator to use a deferred consent procedure defined…as informed consent or permission to continue being involved as a research subject after having been enrolled without either informed consent or permission. In addition, the IRB decided to describe the new consent procedure as "proxy informed consent for continued participation in research" as opposed to using the term "deferred consent." This decision is consistent with Beauchamp's reluctance to use the term "consent" in the expression of "deferred consent" and, instead, [the Board]

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[98] Prentice, E. D., D. L. Antonson, L. G. Leibrock, T. K. Kelso and T. D. Sears (1993). "IRB review of a Phase II randomized clinical trial involving incompetent patients suffering from severe closed head injury." IRB 15(5): 1-7.
[99] Beauchamp, T. L., N. Fost and J. A. Robertson (1980). "The ambiguities of 'deferred consent'." IRB 2(7): 6-9.
[100] Miller, B. L. (1988). "Philosophical, ethical, and legal aspects of resuscitation medicine. I. Deferred consent and justification of resuscitation research." Crit Care Med 16(10): 1059-1062.

proposed the notion of "nondisagreement" with the decisions that have already been made with regard to participation of the subject in the research p3-4[101]

The approach to enrolment for the second PEG-SOD study thus comprised a combination of measures: 1) prospective proxy consent or, in its absence, 2) nondisagreement with decisions already made and 3) proxy informed consent for continued participation. Again this third measure predicted exactly what US EFIC Regulations went on to stipulate two years later in 1996 (see paragraph (b)). This suggests the reasoning used contributed to the rationale for current regulatory measures.

Measures 1) and 3) seem mostly straightforward to justify. Prospective proxy consent manages incapacity of patients and seeks a legal proxy to decide for them, even though contextual difficulties of appointing a competent proxy are not discussed. So too, consent in Measure 3) as only for *continued* participation importantly respects the prospective nature of consent. It avoids suggesting that consent for emergency procedures could be deferred or obtained retrospectively to those procedures being carried out. However, the nondisagreement measure (Measure 2) is under-determined and contradictory of the other two. Non-disagreement, like agreement, retains the same prospective impetus as consent. Agreement is 'to' or 'for' something happening, and even disagreement presumes an existing proposed agreement has not yet been ratified. So nondisagreement does not seem helpful to justify what *has already been done* in the emergency phase.

The nondisagreement measure may simply describe its own limitations as a justifiable solution to enrolment issues. The double-negative of 'nondisagreement' suggests a less

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[101] Prentice et al. (1993) *op.cit.*

demanding measure of agreement than agreement itself. Also nondisagreement conveys a lack of clarity in what one has agreed to – the informational threshold required for the agreement is lower. On the one hand, this lower threshold might be appropriate for decision-making given the urgent context, and might prefigure newer emergency research consent alternatives such as 'informed refusal'[102]. Refusal, like non-disagreement, is also described in a double-negative as '[the] absence of an objection' but not 'a true positive commitment', again pointing to a less demanding threshold for permissible agreement. Yet on the other hand, and unlike nondisagreement, informed refusal should be prospectively given. Furthermore, lowering standard thresholds on a discretionary basis could seem arbitrary and inappropriate to the vulnerability of the emergency cohort. In summary, the non-disagreement measure makes the proposed approach to enrolment less convincing. It does not amount to a justification for enrolment. It also raises questions about the authority of the IRB to approve that approach on a discretionary basis.

Another set of issues in PEG-SOD deals more specifically with discretionary actions and how these resonated with certain parts of the research establishment. In addition to taking discretionary action on consent, the IRB also reinterpreted the minimal risk requirements of the DHHS (referenced as 46.116(d)(1)) such that risk was not minimal with respect to the daily life of a healthy individual, but one with severe closed head injury[103]. However,

[102] Dickert, N. W., A. Llanos and H. Samady (2012). "Re-visiting consent for clinical research on acute myocardial infarction and other emergent conditions." Prog Cardiovasc Dis 55(3): 251-257.
[103] Prentice, E. D., D. L. Antonson, L. G. Leibrock, T. K. Kelso and T. D. Sears (1993). "IRB review of a Phase II randomized clinical trial involving incompetent patients suffering from severe closed head injury." IRB 15(5): 1-7. p6

both reinterpretations led to a regulatory moratorium on emergency research which led to regulation change.

In 1994 PEG-SOD study authors reported that subsequent to the approval of their study in April 1993, the FDA queried its compliance with existing regulations[104]. In response, the FDA required the study sponsor to create an algorithm to demonstrate compliance, defined as:

> a detailed plan describing a sequence of specific steps that are to be followed to reach a particular decision. Use of an algorithm assures that a uniform path, with consistent decision points and rules, is followed in reaching a conclusion that an exception from informed consent is appropriate. p16[105]

The 1994 publication goes on to describe the algorithm in detail, which was 'submitted to each study site for local adaptation and IRB approval'. Importantly, the algorithm was not to help IRBs make decisions about the study, but was to be used 'by investigators' (p16 *ibid*). This indicates that investigators not IRBs were to be responsible for each act of enrolment. The algorithm tries to direct per-patient emergency research enrolment decision-making. In prescribing a formula for investigator decision-making at enrolment, it suggests procedural legitimacy is at the heart of permissibility. Unfortunately for PEG-SOD, the algorithm did not maintain the study's approval, and it became one of a number of studies halted by the Office for protection from research risks (OPRR) in 1993[106]. It became subject to scathing criticism by a 1994 US House Subcommittee report. The report was

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[104] Prentice, E. D., D. L. Antonson, L. G. Leibrock, V. C. Prabhu, T. K. Kelso and T. D. Sears (1994). "An update on the PEG-SOD study involving incompetent subjects: FDA permits an exception to informed consent requirements." Irb 16(1-2): 16-18.
[105] Prentice et al. (1994) *op.cit.*
[106] Biros, M. H., J. W. Runge, R. J. Lewis and C. Doherty (1998). "Emergency medicine and the development of the Food and Drug Administration's final rule on informed consent and waiver of informed consent in emergency research circumstances." Acad Emerg Med 5(4): 359-368.

titled 'Human Guinea Pigs in the Hospital Emergency Rooms; How Some Drug and Device Manufacturers Use Patients Who Can't Say No', and suggested the research was comparable with notorious research exploitation cases from the literature[107].

By the time the PEG-SOD study was halted, existing research regulations were shown to be inadequate for emergency research, certain parts of the research establishment (DHHS, FDA, OPRR, IRB, researchers) disagreed about its permissibility, and the US House Subcommittee had alleged exploitation. Some suggested that variation in interpretation of regulations, and discretionary actions, further complicated this set of issues. If researchers had local community and institutional approval to conduct the research without consent, it was permissible. However, '[c]onversely, if researchers were at institutions that adhered to the literal and regulatory definitions as described by the OPRR, the emergency research could not be performed.' p363-4[108]. On this account, the concerns about approaches to enrolment were increased because researchers and the IRB operated in a discretionary manner, and insufficiently consulted other parts of the research establishment. This was to the detriment of their authority and standing, and impacted other parts of the research establishment.

This case has illustrated researcher and IRB engagement in the issues of enrolment in emergency research. It has shown considered analysis of alternative measures to normal consent, some of which (prospective proxy consent, consent to continued participation measures) will figure in future emergency research regulation. Other measures indicate unsolved ethical enrolment issues (temporally-deferred consent, nondisagreement

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[107] Pappworth, M. H. (1968). Human guinea pigs: experimentation on man, Beacon Press.
[108] Biros (1998) *op.cit.*

measures). Finally it has indicated existing regulations were not fit for purpose in emergency research, even when sensitive reinterpretations of consent and risk were made. IRB authority faltered having made those decisions on its own discretion, and without the approval of certain other parts of the research establishment.

3.4. Case 4: TROICA: altering normal consent in the UK context

The fourth case used is the *Thrombolysis during Resuscitation for Out-of-Hospital Cardiac Arrest (TROICA)* study, a multi-national randomised controlled trial (RCT) of 66 European emergency medical service systems. I include it to show that normal consent in emergency research provoked concern and led to regulatory change in EU Member States as well as the US. TROICA randomised adults in cardiac arrest either to the clot-busting drug tenecteplase or a placebo, at the same time as performing manual resuscitation (chest compressions or CPR). TROICA's attempts to run in the UK encountered regulatory difficulties, and the main study publication appendix shows no recruits from either of the participating UK sites (Cardiff, Wales and Belfast, Northern Ireland)[109,110]. This was because the recently introduced 2004 Regulations, based on the EU Clinical Trials Directive 2001, had prohibited recruitment of emergency patients to clinical trials of investigational medicinal products without prospective informed consent from the patient herself or a

[109] Bottiger, B. W., H. R. Arntz, D. A. Chamberlain, E. Bluhmki, A. Belmans, T. Danays, P. A. Carli, J. A. Adgey, C. Bode and V. Wenzel (2008). "Thrombolysis during resuscitation for out-of-hospital cardiac arrest." N Engl J Med 359(25): 2651-2662..

[110] Dargin, J. M. and L. L. Emlet (2010). "Thrombolysis during out-of-hospital cardiac arrest: a lesson in the law of diminishing returns." Crit Care 14(2): 304.

legal representative [111,112]. This made recruiting UK patients to TROICA illegal and a form of battery. It took an intervention in the House of Lords from Lord Warner, who was at that time the Parliamentary Under-Secretary of State, Department of Health, to amend the UK Regulations[113]. During his statement to the House of 18 Jan 2005, Warner reported that the 2004 Regulations 'require that before an incapacitated person is entered into a clinical trial his or her legal representative must give consent'. This led 'researchers conducting a large international trial in cardiac arrest (the TROICA trial) …[to conclude] that the scheme for establishing the legal representative and obtaining his or her consent is unworkable for clinical trials set in the context of emergency medicine. Thus, it would prove impossible to include United Kingdom patients in such trials unless the UK's requirements were amended.' Warner went on to describe that the relevant regulatory authority would be consulting on changes to the regulations so that patients might be recruited prior to consent from representatives. He cited the government's support for this as being based in protecting participant rights, safety and well-being 'while also ensuring that new treatments for medical emergencies can be developed in the UK'. On this account, the reason to alter the regulations was as much a pragmatic one about supporting the industry of UK research and development as it was an ethical one. The existence of the trial, and

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[111] DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf . For example Article 3 (protection of clinical trial subjects) and Article 5 (clinical trials on incapacitated adults not able to give informed consent). Accessed 26 May 2019.

[112] Medicines for Human Use (Clinical Trials) Regulations. 2004, http://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf . For example, Schedule 1, Part 5 gives conditions for consent from a legal representative of an incapacitated adult. Accessed 19 April 2019.

[113] Lord Warner, House of Lords (2005). HL Deb 18 January 2005, vol 668, Col WS24-5. Available at http://www.publications.parliament.uk/pa/ld200405/ldhansrd/vo050118/text/50118-53.htm#50118-53_head2 . Accessed 15 Nov 2017.

the challenges it raised, was sufficient to question the regulations[114]. As it happened, the trial itself was stopped for futility reasons – the test arm (tenecteplase without adjuvant anti-clotting therapies) offered no improvement over placebo on survival outcomes and increased the rate of intracranial haemorrhage (bleeding inside the skull). Yet the study remains historically significant in terms of shifting regulatory (rather than clinical) paradigms in the UK. Warner's intervention led to an amendment of the regulations published in 2006[115].

Whereas the implementing regulations of the UK prohibited their sites recruiting to TROICA, regulations in other EU Member States were not similarly prohibitive. For example, sites in Germany which recruited n=199 patients to TROICA followed regulations which were based on the same EU Directive. It appears that some editorials and emergency care societies had predicted the directive's deficiencies where emergency research was concerned [116,117]. As a result, they urged emergency researchers in the various member states to influence their own national regulations such that they included an exception to the rule of proxy consent in the case of emergency research. The argument was that it is permissible to study patients without consent or prior proxy consent 'only if the physical/mental condition that prevents obtaining informed consent is an integral characteristic of the research population', as already stipulated in the Declaration of

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[114] Sahan, K. M., K. M. Channon, R. P. Choudhury, R. K. Kharbanda, R. Lee and M. Sheehan (2016). "Refining the Enrolment Process in Emergency Medicine Research." Eur J Cardiovasc Med 4(1): 506-510.
[115] Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006. Statutory Instrument 2006 No 2984. 2006. http://www.legislation.gov.uk/uksi/2006/2984/contents/made. Accessed 19 April 2019.
[116] Sterz, F., A. S. E, B. Bottiger, D. Chamberlain, P. Baskett, L. Bossaert and P. Steen (2002). "A serious threat to evidence based resuscitation within the European Union." Resuscitation 53(3): 237-238.
[117] Kompanje, E. J. O., & Maas, A. I. R. (2004). 'Treat first, ask later?' Emergency research in acute neurology and neurotraumatology in the European Union. Intensive Care Medicine, 30, 168–169.

Helsinki[118,119]. The UK, it appears, was not able to lobby for this exception in time for the deadline implementation of 1 May 2004. As I will describe below, the current 2014 EU Directive does include a specific condition about relatedness of mental capacity to the condition being studied (see Article 35, 1(e) below). It is likely to have been influenced by this prior case and associated discussions.

3.5. Summary of case issues arising so far

The four cases in this section have proven rich sources for ethical issues relevant to the question of justifying decision-making in emergency research. Many of these issues centre on how aspects of normal consent are to be maintained, given the character and context of emergency research. Implicit or explicit suggestions are: 1) retaining the regulative function of normal consent and abandoning a substantive-ethical function (NINDS); 2) prospective proxy consent, or failing that consent to continue participation after the emergency phase, and normal consent in the emergency phase itself, retrospectively obtained (PEG SOD). These suggestions imply that by retaining as much of normal consent as possible, the justification for decision-making is maintained. Other issues relate to more radical attempts to justify the decision-making without any kind of consent in the emergency phase or even beyond. (No consent in the emergency phase will be the core feature of 'waiver of' or 'exception from' consent regulations in emergency research). The following arguments have accompanied such attempts: 1) infeasibility of operating under normal consent due to inherent features of research context or study population (ISIS,

[118] Sterz et al. (2002) *op.cit.* P168
[119] World Medical Association WMA (2000). Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. The 52nd WMA General Assembly, Edinburgh, Scotland, October. 2000. https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2000.pdf Accessed 26 May 2019

TROICA); 2) simplified enrolment procedures as part of a simple design (ISIS); 3) being able to ensure procedural legitimacy (PEG-SOD). The convincingness of these proposed arguments depends on the part regulatory review absent consent plays in the justification. Cases also demonstrated a public dimension to emergency research decision-making, due to the censure of decision-makers who inadequately consulted public bodies. All issues raised are underscored by foundational questions about the authority of deciders involved (roles, responsibilities, credibility).

At this point in the chapter, I pause the case study description to present the emergency research regulations which were implemented in response to the issues raised. This is in order to show how regulations respond to issues which are relevant to the decision-making justification. In Chapter 3, I return to the discussion of case studies using a final case from the post-waiver era of regulation (Case 5: Polyheme).

4. Response from the regulators: new ER-specific regulations

This section sets out how new regulations have responded to ethical issues arising from conducting emergency research. It only describes the regulations in the regulatory jurisdictions pertinent to the above cases (US, EU, UK). There are other emergency research regulations in other jurisdictions and international guidelines which contain some variations[120,121,122]. But broadly they follow the regulations described below, or are less

[120] World Medical Association WMA (2013). Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, 2013 revision, Helsinki. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ Paragraph 30. Accessed 26 May 2019

[121] Council for International Organizations of Medical Sciences (CIOMS) (2016). International Ethical Guidelines for Health-Related Research Involving Humans. Geneva, Switzerland: Council for International Organizations of Medical Sciences https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf. Guideline 16. Accessed 8 April 2019.

[122] CAN (2014). Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, Tri-Council Policy Statement:

demanding to implement. At this stage in the thesis, I do not critically evaluate the regulations (see Chapters 4 and 5 for evaluations). Instead I describe each one by quoting or paraphrasing the relevant sections. In Section 5, I identify themes common to the regulations, or specific to the US EFIC Regulations. This is in order to begin development of the decision-making landscape.

4.1. In the United States (US)

The United States (US) has different regulatory arrangements for emergency research depending on whether the research tests investigational drugs or devices, or therapeutic interventions which are already within the standard of care. The *Exception from the Requirement for Informed consent in Emergency Research (US EFIC) Regulations* apply to FDA-regulated research and regulate investigational drug or device research[123]. The *Waiver of Informed Consent* (*US WIC) Regulations* apply to research not regulated by the FDA (e.g. head to head randomised comparisons of standards of care)[124,125]. The regulations occur in different parts of the US Code of Federal Regulations: 21 CFR § 50.24 for US EFIC, and 45 CFR § 46.116 for US WIC[126,127]. These regulations were implemented in 1996 and were the first ER-specific regulations to come into force, prior to regulations in the UK in 2006 and

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Ethical Conduct for Research Involving Humans, December 2014. http://www.pre.ethics.gc.ca/pdf/eng/tcps2-2014/TCPS_2_FINAL_Web.pdf p41-2. Accessed 8 April 2019.

[123] U.S. Government Food and Drug Administration. Exception from informed consent requirements for emergency research, 21 C.F.R. § 50.24. Available from https://www.ecfr.gov/cgi-bin/ECFR?page=browse Accessed 26 May 2019

[124] Klein, L., J. Moore and M. Biros (2018). "A 20-year Review: The Use of Exception From Informed Consent and Waiver of Informed Consent in Emergency Research." Acad Emerg Med 25(10): 1169-1177.

[125] US-DHHS. The Common Rule. Code of Federal Regulations Title 45 Public Welfare Department of Health and Human Services Part 46 Protection of Human Subjects. 2018. 45 CFR § 46.116 (f)(3)(i). https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html Accessed 26 May 2019

[126] Klein, L. R., B. E. Driver, J. R. Miner, M. L. Martel, M. Hessel, J. D. Collins, G. B. Horton, E. Fagerstrom, R. Satpathy and J. B. Cole (2018). "Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation in the Emergency Department." Ann Emerg Med 72(4): 374-385.

[127] Cole, J. B., J. D. Ho and M. H. Biros (2016). "Randomizing Patients without Consent: Waiver vs Exception from Informed Consent." Prehospital and Disaster Medicine 31(4): 457-458.

the EU in 2014. Although the requirements between US EFIC and US WIC are said to be harmonised[128], the two sets of US regulations carry important basic differences. Firstly, US WIC has a threshold of minimal risk, but US EFIC has no such threshold. Secondly, US EFIC alone has requirements for external (public) and internal (inter-regulatory agency) disclosures and community consultation. (I discuss these requirements in detail in Chapter 3, Section 2). Below I set out both the US EFIC and US WIC Regulations in full:

[128] Klein, L., J. Moore and M. Biros (2018). "A 20-year Review: The Use of Exception From Informed Consent and Waiver of Informed Consent in Emergency Research." Acad Emerg Med 25(10): 1169-1177. See p1170 Table 1 for demonstration of harmonized criteria.

4.1.1. Figure 1: US Exception from informed consent requirements for emergency research

(a) The IRB responsible for the review, approval and continuing review of the clinical investigation described in this section may approve the investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:						
(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.	(2) Obtaining informed consent is not feasible because: (i) The subjects will not be able to give their informed consent as a result of their medical condition; (ii) The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.	(3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) Subjects are facing a life-threatening situation that necessitates intervention; (ii) Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and	(4) The clinical investigation could not practicably be carried out without the waiver.	(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact	(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a	(7) Additional protections of the rights and welfare of the subjects will be provided, including, at least: (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn; (ii) Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the

	(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.	legally authorized representatives and make this information available to the IRB at the time of continuing review.	subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.	clinical investigation, of plans for the investigation and its risks and expected benefits; (iii) Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results; (iv) Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and (v) If obtaining informed consent is not feasible and a legally authorized representative is

	not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.
(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized	

representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

(c) The IRB determinations required by paragraph (a) of this section and the documentation required by paragraph (e) of this section are to be retained by the IRB for at least 3 years after completion of the clinical investigation, and the records shall be accessible for inspection and copying by FDA in accordance with 56.115(b) of this chapter.

(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under 312.30 or 812.35 of this chapter.

(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRB's that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

4.1.2. Figure 2: US Waiver of Consent (US WIC) Regulations from the Common Rule

The 'Common Rule' is the over-arching Federal Policy for the Protection of Human Subjects in research. It outlines the basic provisions for IRBs and informed consent[129]. Subpart A, section §46.116 General requirements for informed consent, details arrangements for 'general waiver or alteration of informed consent' in paragraph (f)[130].

'(f) General waiver or alteration of consent—(1) Waiver. An IRB may waive the requirement to obtain informed consent for research under paragraphs (a) through (c) of this section [i.e. section §46.116], provided the IRB satisfies the requirements of paragraph (f)(3) of this section…'
…
'(f)(3) Requirements for waiver and alteration. In order for an IRB to waive or alter consent as described in this subsection, the IRB must find and document that:
(i) The research involves no more than minimal risk to the subjects;
(ii) The research could not practicably be carried out without the requested waiver or alteration;
(iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
(iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
(v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.'

4.2. In the EU

A new EU clinical trials regulation was published in 2014 which member states should adopt by March 2019[131]. This regulation, unlike its 2001 predecessor, includes provisions for emergency research. The figure below describes and abbreviates the parts of the regulation which are relevant to emergency research:

[129]HHS.gov. (2018). Federal Policy for the Protection of Human Subjects ('Common Rule'). [online] Available at: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html . Accessed 13 Apr. 2019.
[130] US-DHHS (2018). "The Common Rule. Code of Federal Regulations Title 45 Public Welfare Department of Health and Human Services Part 46 Protection of Human Subjects. § 46.116 (f), (f)(3)(i). https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html Accessed 26 May 2019
[131] EU (2014). REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

4.2.1. Figure 3: Regulation (EU) No 536/2014 of the European Parliament

At page L158/3 clause (19), The Regulation recommends emergency trials be authorised by those with 'specific expertise'. This might refer to an ethics committee which is specially trained in emergency research regulatory review.

At page L158/5 clause (36), the Regulation promises to provide 'clear rules concerning informed consent in emergency situations. Such situations relate to cases where for example a patient has suffered a sudden life-threatening medical condition due to multiple traumas, strokes or heart attacks, necessitating immediate medical intervention.'

The fullest explanation of requirements occurs at Article 35 of the Regulation:

'1. *By way of derogation* from [earlier requirements] … , *informed consent* to participate in a clinical trial may be obtained, and information on the clinical trial may be given, *after* the decision to include the subject in the clinical trial, provided that this decision is taken at the time of the first intervention on the subject' (italics and square brackets added for Chapter 3, Section 2.1 discussion below)

The clause above has conditions attached to it. These are (in partial paraphrase) that:

> (a) the situation is urgent and that urgency is caused by a sudden life-threatening or other sudden serious medical condition. Due to this, the participant is unable to provide prior informed consent
> (b) a person's participation is expected to have a 'direct clinically relevant benefit for the subject resulting in a measurable health-related improvement'. This is predicted on scientific grounds
> (c) proxy consent is not possible within the therapeutic window
> (d) the investigator 'certifies' that the patient has not expressed previous objections to participation
> (e) the trial relates directly to the subject's medical condition which in itself has made consent from the subject or her proxy impossible within the therapeutic window; and the trial can be 'conducted exclusively in emergency situations'
> '(f) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition'

2.-3. Consent to continue participation from the subject or her proxy, or objection for use of data already collected in the emergency phase, will be sought after the emergency has passed.

4.3. In the UK

Two pieces of UK legislation cover exceptions from normal consent to emergency research. The first is the *Mental Capacity Act (MCA)*, Sections 30-34 on research[132]. The Act applies in England and Wales but I take it as similarly representative of pieces of legislation covering Scotland and Northern Ireland. The second is the UK-wide *Medicines for Human Use (Clinical Trials) Regulations 2004*, amended twice in 2006 and once in 2008[133,134,135,136].

4.3.1. The Mental Capacity Act (MCA) (England and Wales)

The MCA applies to any research on adult human participants who have mental incapacity where the research does not come under the definition of a clinical trial of an investigational medicinal product (CTIMP)[137]. The definition of mental incapacity in the Act is as follows:

> 2 People who lack capacity
> (1)For the purposes of this Act, a person lacks capacity in relation to a matter if at the material time he is unable to make a decision for himself in relation to the matter because of an impairment of, or a disturbance in the functioning of, the mind or brain.
> (2)It does not matter whether the impairment or disturbance is permanent or temporary.
> (3)A lack of capacity cannot be established merely by reference to—
> (a) a person's age or appearance, or
> (b) a condition of his, or an aspect of his behaviour, which might lead others to make unjustified assumptions about his capacity[138]

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[132] Mental Capacity Act 2005 (c. 9) (2005). Part 1, Research.
[133] Medicines for Human Use (Clinical Trials) Regulations. 2004. http://www.legislation.gov.uk/uksi/2004/1031/contents/made. Accessed 19 April 2019.
[134] Medicines for Human Use (Clinical Trials) Amendment (No.1) Regulations 2006 Statutory Instrument 2006 No 1928. http://www.legislation.gov.uk/uksi/2006/1928/contents/made. Accessed 19 April 2019.
[135] Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006. Statutory Instrument 2006 No 2984. 2006. http://www.legislation.gov.uk/uksi/2006/2984/contents/made. Accessed 19 April 2019.
[136] Medicines for Human Use (Clinical Trials) and Blood Safety and Quality Amendment (No.3) Regulations 2008. Statutory Instrument 2008 No 941. http://www.legislation.gov.uk/uksi/2008/941/contents/made. Accessed 19 April 2019.
[137] For the definition of a CTIMP, see the Medicines and Healthcare Regulatory Agency decision algorithm at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf Accessed 19 April 2019.
[138] Mental Capacity Act 2005 (c. 9) (2005). Part 1, Preliminary, Section 2.

The figure below describes and abbreviates Part 1, Sections 30-34 of the Act which are relevant to the conduct of emergency research.

4.3.2. Figure 4: Part 1, sections 30-34 of the Mental Capacity Act on Research

Section 30 defines what the Act means by research and excludes its application to CTIMP research.
Section 31 puts constraints around the type of research which may be carried out on adults lacking mental capacity:

'31 Requirements for approval
…
(2)The research must be connected with—
(a)an impairing condition affecting P [the patient who lacks mental capacity], or
(b)its treatment.
…
(4)There must be reasonable grounds for believing that research of comparable effectiveness cannot be carried out if the project has to be confined to, or relate only to, persons who have capacity to consent to taking part in it.
(5)The research must—
(a)have the potential to benefit P without imposing on P a burden that is disproportionate to the potential benefit to P, or
(b)be intended to provide knowledge of the causes or treatment of, or of the care of persons affected by, the same or a similar condition.
(6)If the research falls within paragraph (b) of subsection (5) but not within paragraph (a), there must be reasonable grounds for believing—
(a)that the risk to P from taking part in the project is likely to be negligible, and
(b)that anything done to, or in relation to, P will not—
(i)interfere with P's freedom of action or privacy in a significant way, or
(ii)be unduly invasive or restrictive.'

Section 32 covers the responsibilities of researchers who conduct research on adults with mental incapacity, and requires them to take 'reasonable steps' to find a personal consultee, usually a family member, or a nominated consultee, who can give an opinion about the 'wishes and feelings' of the patient about her potential enrolment in the research.
Parts (8) – (10) of this section derogate from these consultee arrangements in the case of research 'as a matter of urgency' ie emergency research:

'(8)Subsection (9) applies if treatment is being, or is about to be, provided for P as a matter of urgency and R considers that, having regard to the nature of the research and of the particular circumstances of the case—
(a)it is also necessary to take action for the purposes of the research as a matter of urgency, but
(b)it is not reasonably practicable to consult under the previous provisions of this section.
(9)R may take the action if—
(a)he has the agreement of a registered medical practitioner who is not involved in the organisation or conduct of the research project, or

(b)where it is not reasonably practicable in the time available to obtain that agreement, he acts in accordance with a procedure approved by the appropriate body at the time when the research project was approved under section 31.
(10)But R may not continue to act in reliance on subsection (9) if he has reasonable grounds for believing that it is no longer necessary to take the action as a matter of urgency.'

Section 33 refers to additional safeguards. It states that:

'nothing may be done' to P 'to which he appears to object (whether by showing signs of resistance or otherwise) except where what is being done is intended to protect him from harm or to reduce or prevent pain or discomfort'.
Advance decisions objecting to research should be respected. P should also be withdrawn if this can be safely done, again 'If he indicates (in any way) that he wishes to be withdrawn' (S33(4)).

Section 34 covers loss of capacity during the research after consent has been given.

4.3.3. The UK Medicines for Human Use (Clinical Trials Regulations) 2004

The regulations will be in force in the UK until 2019 and the adoption of the new EU Clinical Trials Regulation 2014 (as described above)[139]. They apply to CTIMP research on adults who lack capacity, including emergency CTIMPs. The original regulations did not include a provision for emergency CTIMPs but this was altered in subsequent amendments. The figure below shows the parts of the regulations and its amendments which are pertinent to emergency CTIMPs.

4.3.4. Figure 5: Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments

The original 2004 Regulations contain no provision for emergency CTIMPs. However, its second amendment, published in 2006, makes some relevant changes. The changes are to Schedule 1, Part 1 of the Regulations (p39)[140]. The 2nd Amendment directs that:

[139] European Medicines Agency website. Implementation Section. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp Accessed 19 April 2019.
[140] Medicines for Human Use (Clinical Trials) Regulations. 2004. http://www.legislation.gov.uk/uksi/2004/1031/contents/made. Accessed 19 April 2019.

'after sub-paragraph (5) [of p39], insert the following sub-paragraphs—
"(6) Sub-paragraph (7) applies if treatment is being, or is about to be, provided for a subject who is an incapacitated adult as a matter of urgency and, having regard to the nature of the clinical trial and of the particular circumstances of the case—
(a) it is also necessary to take action for the purposes of the clinical trial as a matter of urgency; but
(b) it is not reasonably practicable to meet the conditions [for proxy consent] set out in paragraphs 1 to 5 of Part 5 [p44].
(7) Where this sub-paragraph applies, paragraphs 1 to 5 of Part 5 [p44, proxy consent arrangements] shall not apply in relation to the subject if the action specified in sub-paragraph (6) is carried out in accordance with a procedure approved by an ethics committee or by an appeal panel appointed under Schedule 4 [where an unfavourable original ethics committee opinion was appealed] at the time it gave its favourable opinion."'

Permissible risks for adults in emergency research are the same as for incapacitated adults in Schedule 1, Part 5, sub-paragraphs 9 and 11 of the regulations (p44):

'(9) There are grounds for expecting that administering the medicinal product to be tested in the trial will produce a benefit to the subject outweighing the risks or produce no risk at all…
(11) The clinical trial relates directly to a life-threatening or debilitating clinical condition from which the subject suffers.'

A further amendment in 2008 extends the emergency provisions to CTIMPs which recruit children as subjects. The explanatory note in this amendment says:

'Regulation 4 [of this amendment] amends Schedule 1 to the Clinical Trials Regulations to qualify the application of the requirements… to minors participating in trials. The amendment has the effect that the meeting of those requirements [for proxy consent] can be deferred whilst (i) the minor requires urgent treatment; (ii) urgent action is required for the purposes of the trial; and (iii) meeting the requirements is not reasonably practicable, provided that an ethics committee has given its approval. The requirements in paragraphs 1 to 5 include the requirement of informed consent to be given by a person with parental responsibility for, or a legal representative of, the minor.'

5. Themes common to some or all regulations

Here I identify themes which are common to some or all of the regulations above, by a process of descriptive comparison. All five sets of regulations have the main aim of making it permissible to waive consent for procedures conducted in the emergency phase of the research, provided certain conditions are met. This speaks to a substantial issue relevant

to the decision-making justification: how to operate legitimately when a foundational pillar in the structure of the regulatory model of research ethics is missing, namely the requirement for normal consent. Regulations approach this main aim by decision-making both based on the general profile of the research and its cohort, and based on the specific profile of each participant eligible for enrolment. Other measures such as continued consent after the emergency phase, setting risk thresholds, or (US EFIC) consulting relevant communities or other committees, ostensibly achieve different aims, but in fact also speak to the waiver permissibility aim. For example, requiring consent to continue participation after the emergency phase seems at odds with not requiring consent during the emergency phase. However, this requirement may function to maintain the foundational status of consent (we obtain it where possible), while simultaneously supporting the waiver (we waive consent only where not possible). This reinforces the idea that normal consent is the 'rule' where possible (also a requirement of the regulations), and the waiver is the 'exception' to that rule. By this the waiver may be a defensible proposition, or at least may be less objectionable. Casting the waiver as a permission only to be used in exceptional cases in emergency research might be taken as disingenuous since it mischaracterises a context in which the waiver will nearly always be used. Yet it seems by doing this the waiver regulations aim practically to reconcile the contradictory elements of rule exception (consent waiver) with rule norm (normal consent).

The **first common theme** therefore is satisfying measures by which waiving consent in the emergency phase is permissible. These measures are satisfied by a mixture of general judgements about the research and specific judgements about each participant. General judgments include giving a scientific rationale for only being able to use incapacitated emergency patients to answer the research question (US EFIC (a)(1), EU Article 35(1)(e),

UK MCA Section 31(2) and (4)). The fact of, and reason why, patients cannot give consent is also stipulated, either because of their medical condition, or because their condition is linked in with their incapacity and need for urgent treatment (US EFIC (2)(i), EU Article 35(1)(e)). The regulatory review body (REC or IRB) which makes such general judgements is implied to have a certain specific expertise (EU page L158/3 clause (19) 'specific [ethics committee] expertise'), or combine its own decision-making with that of a 'licensed physician' who is independent of the project (US EFIC (a)).

Specific judgements include physician-researchers deciding per participant whether or not consent is possible. This is through a decision-making process (see second theme below). In deciding whether consent waivers apply, it is common for the language of practicability or feasibility to be used (US EFIC (a)(2),(4),(6),(7)(v), US WIC (f)(3)(ii), UK MCA S32 (9)(b), UK Regs Part 1 (6)(b)).

Subsequent themes relate to the aim of the first theme more or less directly, having also their own discrete, different aims. I designate **the second common theme** as an off-shoot of the first theme, since it comprises the process and roles which accompany specific judgements to ensure that the waiver applies at the level of individual participant enrolment. It requires the preparation of certain consent documents and documenting of certain consent and consent waiver processes. These include preparing normal consent documents in case normal consent or proxy consent is possible in certain cases (US EFIC (a)(6), UK MCA guidance pages[141]). Researchers should first assess each participant for

[141] Health Research Authority, Mental Capacity Act guidance page, last updated 19 Mar 2018 > Applying for Approval Under the Act http://www.hra.nhs.uk/resources/research-legislation-and-governance/questions-and-answers-mental-capacity-act-2005/ . Accessed 19 April 2019.

ability to give normal consent. If this is not possible, they should attempt to find legal proxies, and lastly attempt to find a family member or other legal representative (US EFIC (a)(7)(v), EU 1. (c-e), UK MCA S32 (8)(b) and (9)(a), UK Regs Part 1 (6)(b)). Available proxies may variously consent to the research on the patient's behalf (US EFIC (a)(5), EU 1.(c)), give an opinion about his wishes or feelings with respect to enrolment (UK MCA S32), or object to his inclusion (US EFIC (a)(6)). The EU Regulations also require the researcher to 'certify' that the patient himself has not expressed prior objections to enrolment in research (EU 1.(d)). Any elicited proxy judgement means consent cannot be waived. These attempts should be documented. This is so that IRBs can perform interim or 'continuing review' of the process (US EFIC (a)(5) and (a)(7)(v)). It is implied that researchers should follow IRB-approved processes for informing proxies of patient study inclusion and options for study discontinuation (US EFIC (b), US WIC (f)(v), EU 2-3).

This second theme is explicit about who undertakes which roles in order to satisfy the requirements for individual level assessment. The physician-researcher is responsible for implementing attempts at consent or proxy consent, and deploying the waiver in individual cases. If proxy consent is possible, this is a decision-making task for legal proxies including independent medical professionals, or non-legal proxies (US EFIC (a)(5),(6) and (7)(v), EU 1.(c), UK MCA S32 (9)(a)). The IRB or REC has both a pre-study and mid-study role. It approves documentation and the process in principle (US EFIC (a)(6)), and also monitors the enacted process via 'continuing review' (US EFIC (a)(5)). Furthermore it is responsible for keeping the judgements about individual waiver permissions on file (US EFIC (c)).

The **third common theme** is the requirement for risks and benefits to be judged and decided in certain ways. It seems intended to support the first theme indirectly: by setting

risks and benefits at reasonable ratios and thresholds, this supports waiver permissibility. Risks and benefits are described in both relative and absolute terms in the regulations. Relative risk and benefit terms used are: 'direct' or 'directly clinically relevant' benefit; risks which are 'reasonable in relation' or 'in comparison'; and burdens which are not 'disproportionate'. Absolute risk and benefit terms are fewer. US WIC Regulations require that 'The research involves no more than minimal risk to the subjects'. EU Regulations state the clinical trial should pose a 'minimal risk to, and…minimal burden on, the subject' yet minimal risk is still calculated by comparison with the 'standard treatment of the subject's condition' (EU 1.(f)). The UK MCA also states that if there are no potential benefits for the participant in the research, then risks to him should be assessed as 'negligible' (UK MCA S31 (6)(a)).

Risks and benefits are not usually associated with specific types of research activity. Instead they are referred to generally as risks or benefits of certain enterprises. These are termed: 'participation' (US EFIC (a)(3), EU 1.(b), UK MCA S31(6)(a)); the 'investigation' or 'activity' (US (a)(3)(iii); 'the clinical trial' (EU 1.(f)); or 'the research' (UK MCA S31(5)(a)). The UK and US EFIC Regulations, however, do associate risks and benefits with specific features of the research and its population, such as the risks of therapeutic procedures. The UK Regulations say there should be grounds for expecting that administering the test medicinal product will produce benefit on net or 'no risk at all' (see Figure 5, clause (9) above). The US EFIC Regulations refer to the risk-benefit ratios of i) 'standard therapy', and ii) the 'proposed intervention or activity' (US EFIC (a)(3)(iii)). 'Proposed intervention or activity' may reference test therapeutic procedures, even though not explicitly. By this the UK and US EFIC Regulations give some suggestion of how risks and benefits should be more specifically judged and decided in the research. Potential for therapeutic design research

to offer some kind of therapeutic benefit for participants is a requirement in four sets of regulations (US EFIC (a)(3), EU 1.(b), UK Regs Part 5 (9), MCA S31(5)(a)).

6. Themes specific to the US EFIC Regulations

The fourth and fifth themes are specific to the US EFIC Regulations. However, they connect to issues which have arisen in prior cases above, and will connect to issues discussed in a final case in Chapter 3 (Case 5: Polyheme). The **fourth theme** is external (public) and internal (research establishment[142]) disclosures about the research. These are often lumped with discussions of the requirement to consult relevant communities about the research[143,144]. Yet disclosures may have different functions from consultation. For instance, they involve different audiences (the public, parts of the research establishment, and the community), and have different aims. Therefore, lumping may obscure the different functions. For this reason, I shall discuss disclosures separately in the thesis.

Before the research, external or 'public' disclosures are to communities who comprise the community consultation in a7i. This is because they are described in the same way in both a7i (consultation) and a7ii-iii (disclosure) requirements as 'communities in which the clinical investigation will be conducted and from which the subjects will be drawn'. After the research, public disclosures are to those communities once more, and also researchers (US EFIC (a)(7)(ii-iii)). Interestingly post-research disclosures are to apprise of study features, specifically the demographic characteristics of the research population, and the

[142] By 'research establishment' I mean those with professional stakes in the research such as researchers, IRBs, Sponsors, commercial partners, or consultants such as lawyers

[143] Richardson, L. D., R. Rhodes, D. F. Ragin and I. Wilets (2006). "The role of community consultation in the ethical conduct of research without consent." Am J Bioeth 6(3): 33-35; discussion W46-50. See for example p33 where the authors mention 'public disclosure' and 'public notification' alongside community consultation, but go on only to talk about community consultation.

[144] Dickert, N. W. and J. Sugarman (2007). "Getting the ethics right regarding research in the emergency setting: lessons from the PolyHeme study." Kennedy Inst Ethics J 17(2): 153-169. P159.

research's results (US EFIC (a)(7)(iii)). Although the same community audience is referenced in both disclosure and consultation requirements, describing disclosures as 'public' here suggests a broader community or wider public is the intended recipient of the disclosures.

Internal disclosures are from data monitoring committees to the IRB and researchers about interim safety data findings (US EFIC (a)(7)(iv)). They are also from the IRB itself to the Research Sponsor and researchers, sharing their judgement about unsuccessful applications to conduct the research under the waiver (US EFIC (e)). In turn, the Sponsor has to make a further substantial set of internal disclosures. It should disclose the IRB's 'unsuccessful' judgement about the research to: 1) all actual or potential participating centres in the research or in 'substantially equivalent' research under its auspices; 2) all other IRBs involved in centre-level reviews of the research or substantially equivalent research; and 3) the clinical trials regulator, the FDA.

The **fifth theme** is the requirement for consultations with communities who may be affected by the research, or whose members may be enrolled to the research (US EFIC (a)(7)(i)). Although the requirement under this theme is exclusive to the US EFIC Regulations, it is also being used *ad hoc* in other jurisdictions[145]. This theme also seems contributory to the first theme above. This is because consultations should state that consent will not be obtained, at least in the emergency phase (see Community consultation theme section below). In addition, it seems to support the third theme, acceptability of

[145] UK Paramedic 2 trial website. This trial provided opt out mechanisms which are associated with a community consultation even though this was not a regulatory requirement. https://warwick.ac.uk/fac/sci/med/research/ctu/trials/critical/paramedic2/nostudy/

research risks, because it is described as a part of 'additional protections of the rights and welfare of subjects' which specifically involves disclosure of 'expected risks and benefits' (US EFIC (a)(7),(ii)).

7. Chapter Conclusion

In this chapter I firstly noted the advancements in emergency medicine wrought by emergency research to date. Secondly, I highlighted the innate challenges which emergency medicine and so research poses for the regulatory model of research ethics. Thirdly, I presented four cases (NINDS, ISIS, PEG-SOD and TROICA) and highlighted issues they raised which are relevant to the question of justifying emergency research decision-making. Attempts made by researchers and regulators in these cases to retain normal consent were unsuccessful, as were more radical attempts to waive consent on a discretionary basis. Cases also demonstrated a public dimension to the issues of justifying decision-making. Fourthly, I set out regulations specific to emergency research which were introduced in response to these cases. Regulations commence the dialogue between cases and regulations which spans this chapter and Chapter 3. Finally, I identified themes common to the regulations by a process of descriptive comparison. The themes were: 1) presuming waiving consent is permissible; 2) ensuring waiving consent is permissible; and 3) acceptability of risks and benefits. I also drew two additional themes from the US EFIC Regulations: (4) external and internal disclosures; and 5) community consultation). This commences the mapping of the decision-making landscape. In Chapter 3, I shall complete full theme development and mapping of the landscape using conceptual analysis.

Chapter 3: Developing themes and characterising the decision-making landscape fully

1. Introduction

In this chapter, I develop the five themes identified in Chapter 2. Using conceptual analysis, I link themes to issues raised by case studies in Chapter 2 and this chapter. This results in five fully-developed themes, and so completes my characterisation of a critical landscape relevant to the question of justifying decision-making in emergency research. By referring to themes and thematic analysis here in the chapter, I mean a conceptual analysis approach involving comparative and thematic work, but not a formal thematic analysis as used in qualitative research.

This chapter also contains analysis of the final case study, Case 5: Polyheme, a case widely discussed in the bioethics literature which raises further key issues relevant to decision-making. I place this case in this chapter to reflect the overarching structure which spans Chapters 2 and 3 as a dialogue between cases and regulations. Case 5 responds to the introduction of the US EFIC Regulations and their extra requirements for disclosures and community consultation.

I conclude the chapter by highlighting a chief finding represented by Themes 1 and 2. These themes reflect a potentially justifiable decision-making strategy which reconciles the use of consent waivers with consent. The strategy depends on harmonizing two areas of decision-making: 1) prior to the research at the general level of regulatory review; and 2) at the individual level of participant enrolment to the emergency phase of the research.

2. Developing regulatory themes using conceptual analysis

In this section I conduct conceptual analysis of Chapter 2 regulatory themes. This is by linking themes to issues from cases and using further implementation guidance and conceptual literature where appropriate. This is in order to develop the themes further, and so complete my characterisation of the decision-making landscape. The resulting fully-developed themes establish a focus within the thesis on justifying decision-making based on the requirements of the US EFIC Regulations. These regulations represent the more demanding justification challenge to address within the thesis. This is because they have extra requirements for disclosures and community consultation (Themes 4 and 5) which present particular resource and implementation challenges. By this focus, I address the more demanding challenge and so aim to develop the strongest set of arguments in subsequent chapters for justifying decision-making.

2.1. Theme 1: Presuming waiving consent is permissible

I have said this theme speaks to the main aim of the regulations to permit a waiver of consent for procedures conducted in the emergency phase of the research. This theme connects to other themes which ostensibly achieve different aims, but are contributory to permitting the waiver itself. I also said this main aim was achieved by a combination of both general-level assessments about the research and individual-level assessments of individual participants.

Decision-makers in all four cases above (see Chapter 2, Section 3 case discussion) faced issues over how to incorporate normal consent (or alternatives) into the context of the research appropriately, and how to waive consent permissibly. For example, the NINDS case practised normal consent in a research context which was not amenable to normal consent. Alternatively, the ISIS case practised consent waivers in a regulatory context

which did not permit this. Authors of the regulations have responded by permitting the waiver under conditions in the emergency phase of the research, and also retaining the possibility for normal consent. In this way, they suggest that consent waivers are permissible in some but not all enrolment instances. In doing this, I argue that they aim practically to reconcile, per participant, the contradictory elements of rule exception (consent waiver) with rule norm (consent). This strategy is potentially an improvement on using the deferred consent concept discussed as illegitimate in the PEG-SOD Case (see Chapter 2, Section 3.3) [146]. This is because it does not claim to obtain consent where the consent waiver is permissible, but it also retains the option for consent where it is possible.

This proposed decision-making strategy relies on reconciliation happening in practice. This is by the combination of decision-making at the general level and the individual level. General-level decision-making presumes the research is permissible in principle under the waiver. Individual-level decision-making ensures the waiver is permissible, and if not deploys measures for normal (or proxy) consent (see Theme 2 below). However, general-level decision-making may influence individual-level decision-making in a way unintended by this strategy. Securing permission in principle for the waiver at regulatory review and prior to any enrolment instances may be taken to obviate the need for individual level assessment. In doing this, the general-level decision-making may function to avoid or discourage ensuring that a waiver is permissible (and if not permissible then reverting to a form of consent). As a result, permissibility of the waiver would not be *ensured* as well as presumed, but rather wholly *presumed*. The reconciliation strategy would thus falter.

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[146] Beauchamp, T. L., N. Fost and J. A. Robertson (1980). "The ambiguities of 'deferred consent'." IRB 2(7): 6-9.

The unintended influence of general- over individual-level decision-making is a risk given certain examples of specific terms and clauses within the regulations. The first example of this comes from the most recent 2014 EU Regulations. They are poised to be highly influential on the practice of emergency research and the justification of the consent waiver in all twenty-eight EU Member States (at time of writing in April 2019). Yet they revert to advocating deferred consent as a legitimate concept. Article 35 1. implies that informed consent can be obtained from the participant retrospectively – after inclusion and after the decision to administer the first research intervention. The 'derogation' is the exception from the rule norm of consent. By reverting to deferred consent, the contradictory elements of rule exception (consent waiver) and rule norm (consent) become conflated and so mutually incoherent. Yet advocates for this type of 'treat first, ask later' approach persist in the EU emergency research literature [147,148].

The second example of unintended influence occurs in the language of practicability and feasibility in the regulations. For example, 'the research could not be practicably carried out without the waiver' (US EFIC (a)(4)) suggests general level assessment determines practicability to conduct research under the waiver. However, clauses referring to it being 'not reasonably practicable' or 'feasible' to obtain (proxy) consent (UK MCA S32(8)(b), UK Regs Part 1 (6)(b), US EFIC (a)(2)) suggest individual level assessment determines practicability to enrol specific patients under the waiver. On this account, practicability and feasibility relate both to general and individual level assessments of

[147] Kompanje, E. J. and A. I. Maas (2004). "'Treat first, ask later?' Emergency research in acute neurology and neurotraumatology in the European Union." Intensive Care Med 30(1): 168-169.
[148] Mentzelopoulos, S. D., et al. (2015). "Evolution of European Union legislation on emergency research." Resuscitation 91: 84-91.

waiver permissibility. Yet a number of factors resist individual assessment in practice. Firstly, (reasonable) practicability and feasibility convey latitude and generality with respect to fulfilling the relevant regulatory requirements. As terms they seem counter to the giving of specific reasons or the conduct of individual assessments in order to be fulfilled. This lends their fulfilment to decision-making at the general level, where details of individual participants are unknown. Secondly, cases such as ISIS have indicated that a practicable or simple approach to emergency research entails substantial streamlining or omission of individual-level enrolment processes. Feasibility and practicability therefore seem emblematic of a subtle unintended influence of general- over individual-level decision-making.

The third example of unintended influence is a baseline presumption about the general mental capacity profile of the participant cohort, given their life-threatening condition and the emergency context. This is seen in the UK emergency research regulations of the *UK Mental Capacity Act*. The primary guiding principle of the Act is a presumption of capacity and maximising a person's ability to make decisions himself. This is expressed in Part 1, Section 1 of the Act:

> (2)A person must be assumed to have capacity unless it is established that he lacks capacity.
>
> (3)A person is not to be treated as unable to make a decision unless all practicable steps to help him to do so have been taken without success[149].

The principle empowers individuals with mental health issues when undergoing treatment or research. It suggests we should always individually assess a person before

[149] Mental Capacity Act 2005 (c. 9) (2005). Part 1, Principles, Sections (2)-(3)

deciding he is mentally incapable. Yet in the case of emergency research, the Act's waiver provisions appear to go against this, by presuming incapacity to consent due to context. This is chiefly demonstrated by the clause which states:

> (4)There must be reasonable grounds for believing that research of comparable effectiveness cannot be carried out if the project has to be confined to, or relate only to, persons who have capacity to consent to taking part in it [150]

The clause indicates that we should not conduct planned emergency research under the waiver if we can do research which achieves a comparable result using those with capacity. We should also not use an incapacitated population to inform treatment of conditions suffered by people with capacity, as this unfairly burdens the population. The clause intends to limit the emergency research conducted under the waiver to that which is essential. However, it may also indicate that for the research to be permissible it cannot be the case that anyone within the emergency patient cohort is found to have capacity in practice. This would disprove the basis for presuming the waiver permissible (so casting doubt over the decision-making) and also risk rolling back approval for the research. Individual assessment becomes a potential contradiction to general level assessment, and also risks thwarting the research if approval is rolled back.

The US EFIC Regulations also contain a variant on this presumption about the general mental capacity profile of the participant cohort:

> (2) Obtaining informed consent is not feasible because: (i) The subjects will not be able to give their informed consent as a result of their medical condition (US EFIC (a)(2)(i))

[150] Mental Capacity Act 2005 (c. 9) (2005). Part 1, Research, Section 31(4)

Tying consent infeasibility to medical condition furthers a presumptive basis for insufficient capacity. The logic is as follows: if all must suffer from the medical condition of interest in order to be eligible for the study, then all must have insufficient capacity to consent. Being able to presume incapacity because it is an 'integral characteristic' of the population under study was also the rationale for permitting a waiver of consent in the TROICA Case. While there may be reasons to support a degree of presumption about the waiver permissibility in individual cases (e.g. we don't want to waste valuable time checking whether a participant is incapacitated[151]), the influence of the presumption here seems at risk of sidestepping the process of ensuring permissibility altogether.

Taking general level assessments to obviate the need for individual level assessments undermines decision-making at the individual level of specific instances of enrolment. The decision-making (carried out by the physician-researcher) seems superfluous if the permissibility of the waiver is wholly on a presumed basis. This was the implication of the ISIS case above.

Characterising the issues further under this theme has revealed that regulations may be pursuing a reconciliation strategy between waiving consent and obtaining consent. However, the strategy stands in need of clarification. In particular, unintended influence of general over individual decision-making risks side-lining individual level assessment, so thwarting the strategy.

[151] Roberts, I., D. Prieto-Merino, H. Shakur, I. Chalmers and J. Nicholl (2011). "Effect of consent rituals on mortality in emergency care research." Lancet 377(9771): 1071-1072.

2.2.Theme 2: Ensuring the waiver is permissible: process and role

As discussed above, Theme 2 is a crucial part of the proposed reconciliation strategy: it comprises individual-level decision-making in order to ensure the waiver is permissible. If it is not permissible, measures for normal (or proxy) consent are deployed. Decision-making occurs via a formal process with designated roles. The physician-researcher is given substantial responsibility for undertaking the process; she should check that normal (proxy) consent is not possible, document her failed attempts, and ultimately make (and document) the decision to enrol the participant on a consent waiver. In doing this, the regulations may expect the physician-researcher to use her experience of negotiating her care-research role in order to inform decision-making[152]. The process echoes the proposed algorithmic decision-making as in the PEG-SOD Case above, suggesting that deliberateness and consistency of process is important. Also it rejects the inference in the ISIS Case that decision-making at emergency enrolment is not ethically valuable, and that emergency enrolment does not merit a deliberate process which is documented. Documents and documentation facilitate attempts at forms of normal consent, register or disclose objections, and record the waiver instances themselves. By this they ensure waiving consent is permissible. They also monitor overall regulatory compliance.

Yet the regulations are less clear about content of the documentation. US EFIC Regulations state that researchers should only 'summarise efforts' to contact proxies or other family members, but this still gives little indication of the content involved. We can imagine the diligent researcher trying to record quantitative data (e.g. dates and times of phone numbers dialled) as well as qualitative data about conclusions they drew from

[152] See Chapter 1, Section 4 for how I understand the researcher as the physician-researcher in the thesis

conversations with shocked family members, all the while dealing with the emergency admission and the research protocol. We can also imagine the reverse, where researchers pay only lip service to the process. It also seems the regulations might be clearer about why the counter-intuitive act of documenting a failed attempt at something is important, namely recording the absence of obtained consent. Similarly, the preparation of normal consent documents such as patient information sheets seems superfluous, unless it is understood as an important part of the strategy to reconcile rule exception with rule norm, enacted during the process of ensuring the waiver at the individual level.

2.3.Theme 3: Acceptability of risks and benefits

Risk judgements and decision-making mostly contribute to the first theme of presuming the waiver is permissible. This is because risks are characterised and calculated as part of the general research profile, and the general characteristics of the research cohort (lacking capacity and vulnerability to harm). Risk calculations therefore protect patients as a grouped cohort, given consent will probably be absent and thus a patient's ability to protect *his own* welfare, and consider whether risks are acceptable *to him*, is absent.

Issues relevant to decision-making about acceptable research risks have rarely arisen in the case studies in Chapter 2 (see Chapter 2, Section 3). Only the IRB in Case 3 (PEG-SOD) found calculating risk to be an issue, and reinterpreted minimal risk requirements which were in place prior to the incoming 1996 US EFIC Regulations. The IRB's rationale was a concern that a threshold of minimal risk would apply to the daily life of a healthy person rather than a person with severe head injury, and so prevent the research from being approved. They therefore decided to make minimal risk relative to illness severity. McRae and Weijer's justification of emergency research, based on a risk algorithm, criticises this

decision which also influenced the future US EFIC Regulations[153]. The authors point out that a minimal risk threshold should properly only apply to the risks of non-therapeutic procedures, and should not be calculated relative to illness severity[154]. However, initial misinterpretations about this have led to the omission of minimal risk from the US EFIC Regulations in favour of 'reasonable risk'. As a result, judging reasonable risk has become too permissive of risk in emergency research for two reasons.

Firstly, the judgement does not specify whether a given procedure in the calculation is therapeutic or nontherapeutic. This does not appropriately organise research and clinical comparators into therapeutic and nontherapeutic categories. Inappropriate trade-offs can occur as a result, such as the risks of non-therapeutic procedures being traded against the benefits of therapeutic procedures. McRae and Weijer argue this is inappropriate since non-therapeutic procedures cannot be offset by prospect of therapeutic benefits.

Secondly, linking research risks to 'severity of the patient's clinical condition' without a cap on risk means that by virtue of illness severity an emergency patient could be exposed to very high risks[155,156]. On their account, this is problematic because it exploits the vulnerability of the emergency research patient cohort.

McRae's and Weijer's criticisms are illustrated by a tendency in the emergency research regulations to under-specify type of risks, referring to risks of 'participation', 'the

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[153] McRae, A. D. and C. Weijer (2002). "Lessons from everyday lives: a moral justification for acute care research." Crit Care Med 30(5): 1146-1151.
[154] McRae and Weijer 2002 op cit p1146. The authors quote 45 CFR 46.116d, although as of 2018 the appropriate reference is 45 CFR § 46.116f3i.
[155] McRae and Weijer (2002) *op. cit.*
[156] Weijer, C. and P. B. Miller (2004). "When are research risks reasonable in relation to anticipated benefits?" Nat Med 10(6): 570-573.

investigation', or the 'activity'. Even though the US EFIC Regulations refer to specific features of the research and its population in deciding risks, these features are grouped in the overall comparative risk calculation. In regulations with a threshold of minimal risk (US WIC, and EU Regulations), the threshold is applied to the participant, and does not indicate we should calculate risk with strict reference only to the research's nontherapeutic procedures. Only the UK regulations specifically require therapeutic procedures to produce clinical benefit[157].

The account by McRae and Weijer calls for more precision in risk assessments to avoid misinterpretation and excessive risk. They indicate precision may be achieved procedurally by the IRB using an algorithm, so acting as a social mechanism to determine risks and protect research participants[158]. This supports the idea in Theme 1 that by making decisions at the general level, in this case about whether risks are permissible, we may presume that the waiver is permissible. This presumption is further demonstrated by the concept of clinical equipoise, a key step in the calculation of therapeutic risks within their algorithm. Equipoise requires maintenance of formal, theoretical uncertainty and disagreement about test treatment superiority[159]. Specific, practical checks about how risks will affect a given participant are antithetical to this concept.

Yet by leaving risk determinations to general level presumptions, uncertainty remains over how to interpret certain qualifiers of risk within the regulations. Take the UK Mental

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[157] See Chapter 2, Section 4.3.4, UK Regs Part 5 (9) which states that 'There are grounds for expecting that administering the medicinal product to be tested in the trial will produce a benefit to the subject outweighing the risks or produce no risk at all…'
[158] McRae and Weijer (2002) *op. cit.* p1150
[159] McRae, A. and Weijer, C. (2008), U.S. Federal Regulations for Emergency Research: A Practical Guide and Commentary. Academic Emergency Medicine, 15: 88–97. doi:10.1111/j.1553-2712.2007.00001.x Figure 1.

Capacity Act, where nontherapeutic research risks should be 'negligible' and procedures should not be 'unduly invasive or restrictive' (UK MCA 31(6)(a), (b) (ii)). There is no guidance about how to interpret the qualifiers 'negligible' and 'unduly' within a risk calculation at the general level of regulatory review. The qualifiers may suggest applying extra caution to any risk judgements made. However, they seem too indeterminate as terms to aid general level consideration in a meaningful way. This may mean they are more meaningfully applied at the level of individual patient assessments. As with Theme 1, this generates a question about how far general decision-making should determine and influence what is permissible in particular individuals. What justifies those at the general level to authorise an individual's exposure to a set of research risks?

2.4. Theme 4: External (public) and internal (research establishment) disclosures

US EFIC Regulations have instituted requirements for pre- and post-research public disclosures. These regulations also require internal disclosures to share unsuccessful application attempts, and other data about completed studies, between different actors within the research establishment. They are alone among the regulations described in Section 4 of this chapter in requiring such disclosures. Disclosures further characterise issues arising in the case studies in this Chapter (both above and below this section). Issues relate to both wider acceptability of the waiver (external disclosures) and communication and information-sharing between parts of the research establishment (internal disclosures) (see Chapter 2, Section 3, Case 3: PEG-SOD above and Case 5: Polyheme below).

The public disclosure requirement is described most fully in FDA guidance as:

> dissemination of information (i.e., one-way communication) to the community(ies), the public, and researchers about the emergency research.
>
> The goal of public disclosure prior to initiation of the study is to provide sufficient information to allow a reasonable assumption that the broader community is aware of the plans for the investigation, its risks and expected benefits (see 21 CFR 50.24(a)(7)(ii)), and the fact that the study will be conducted without obtaining informed consent from most study subjects.
>
> The goal of public disclosure (PD) after the study is completed is to ensure transparency: that the communities, the public, and scientific researchers are aware of the study's results. Disclosure to researchers of the results, both positive and negative, of studies conducted under [the US EFIC Regulations] is particularly important because such disclosure may help FDA and researchers learn from these studies involving vulnerable subjects who are unable to consent p34-5[160].

I noted above that although disclosures are 'public', they reference only the same community as described in the community consultation requirement. The guidance above confirms the implication that this same community is conceived as 'wider' for the purposes of disclosure than for consultation itself. The guidance suggests also that wider public awareness is the chief function of public disclosure. There is not only a need for community consultation, but also 'broader community' awareness of plans through public disclosures. Specifically, the disclosure should allow for 'assumption' of awareness of plans for the research. This seems in service of the main aim to permit the waiver, but sits somewhere between presuming and ensuring that the waiver is permissible (Themes 1 and 2). Prior disclosure does not seek specific agreements from the community, but it allows, through an assumption of community awareness, a presumption that the research is permissible under the waiver.

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[160] FDA Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research. (April 2013 version). Available at: https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf Accessed 19 April 2019.

The content of public disclosures may also speak to Theme 3, risk assessments, since they disclose information about risks. Given the negative treatment of the PEG-SOD case (and the Polyheme case: see below) in the public discourse, it is perhaps understandable that a requirement for public disclosure and notification exists, particularly notification prior to the study start. However, there is much debate in the literature about the form and extent of the requirement, including how many disclosures should be made, and what resources should be devoted[161,162,163]. This is part of a lack of conceptual clarity in the literature around public disclosure and notification as a specific requirement, rather than as lumped with the consultation requirement. It does appear, however, that public disclosure is a one-way communication of information, aimed at the community but resonating more widely than the community. This wider resonance might also entail a difference between the reach and scope of information communicated in disclosure, and that in consultation.

The FDA guidance above also makes reference to the internal disclosure requirement. This requires disclosures between different actors within the research establishment, for example communication between IRBs, or between the Sponsor and the FDA. Firstly, this suggests that emergency research may be susceptible to suppression of negative results, or of unsuccessful regulatory review applications. The latter will be illustrated by the final case study (see Case 5: Polyheme below). Secondly, it reflects a need to manage complexity

[161] Salzman, J. G., et al. (2007). "Implementing emergency research requiring exception from informed consent, community consultation, and public disclosure." Annals of Emergency Medicine 50(4): 448-455.
[162] Stephens, S. W., et al. (2016). "Using social media for community consultation and public disclosure in exception from informed consent trials." J Trauma Acute Care Surg 80(6): 1005-1009.
[163] Matchett, G., et al. (2018). "Measuring the cost and effect of current community consultation and public disclosure techniques in emergency care research." Resuscitation 128: 37-42.

of the multiple regulatory processes which might occur in certain cases of the research[164]. This is to avoid contradicting judgements given by different processes, as evidenced in the PEG-SOD case above. It is also to avoid applicants to these processes trying to game the system (as in Case 5: Polyheme below). By doing this, it may help to maintain the credibility of the research establishment, which was compromised in the PEG SOD and ISIS cases. Thirdly, the above guidance indicates a stronger duty than normal to publish any results (positive or negative) arising from emergency research studies. It is unusual to find data sharing and dissemination as a requirement of ethics regulation, as opposed to a requirement or advisory of research integrity codes of conduct, e.g. ICMJE good publishing standards [165] . Data sharing to avoid duplication of studies may refer to a further requirement within Theme 1 that the research and proposed waiver be necessary in the proposed emergency cohort (US Regs a1, EU Article 35(1)(e)). Internal disclosure within the research establishment, and to researchers as part of public disclosure of study results, may help limit the use of such cohorts.

2.5.Theme 5: Community consultation

US EFIC Regulations are also unique in instituting a requirement for consulting relevant communities about proposed research. The community consultation requirement does not seem directly linked, or in response, to issues arising from the cases above[166]. Neither does

[164] Kipnis, K., N. M. King and R. M. Nelson (2006). "Trials and errors: barriers to oversight of research conducted under the emergency research consent waiver." Irb 28(2): 16-19. Authors argue that the Polyheme study Sponsor (Northfield) tried to withhold information. Other sites in the study withdrew ethics applications if it seemed likely that the IRB would disallow the study

[165] Taichman, D. B., P. Sahni, A. Pinborg, L. Peiperl, C. Laine, A. James, S.-T. Hong, A. Haileamlak, L. Gollogly, F. Godlee, F. A. Frizelle, F. Florenzano, J. M. Drazen, H. Bauchner, C. Baethge and J. Backus (2017). "Data sharing statements for clinical trials: a requirement of the International Committee of Medical Journal Editors." The Lancet 389(10086): e12-e14.

[166] It could be taken to relate to political controversy in the PEG-SOD case, but this controversy does not seem to motivate a direct response from the community itself.

it seem to refer to issues in the emergency research literature which preceded the introduction of the regulations. However, in being part of the new emergency research regulations, it will go on to relate to other issues raised (see Case 5: Polyheme below). The work of the thesis is then to examine how these issues relate to the decision-making justification. Halperin et al. writing in the journal *Circulation* give the goals of community consultation as:

> (1) to explain the nature of the research, with its attendant risks and benefits; (2) to state that informed consent will not be obtained from individual subjects before study participation; and (3) to explain the process by which potential subjects can refuse to participate in research studies p1856[167]

Similarly, from the actual clause describing the requirement, it is understood as an 'additional protection' of the 'rights and welfare of subjects' (US Regs (a)(7)). The FDA guidance on the US emergency research regulations, updated in 2013, goes into further detail:

> Community consultation activities should be designed to help ensure that the communities in which the emergency research will be conducted and from which subjects will be drawn are adequately informed about the risks and expected benefits of the research and are given the opportunity to ask questions about it, and express their views prior to the IRB making a determination about the research p16[168].

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[167] Halperin, H., N. Paradis, V. Mosesso, Jr., G. Nichol, M. Sayre, J. P. Ornato, M. Gerardi, V. M. Nadkarni, R. Berg, L. Becker, M. Siegler, M. Collins, C. B. Cairns, M. H. Biros, T. Vanden Hoek and M. A. Peberdy (2007). "Recommendations for implementation of community consultation and public disclosure under the Food and Drug Administration's "Exception from informed consent requirements for emergency research": a special report from the American Heart Association Emergency Cardiovascular Care Committee and Council on Cardiopulmonary, Perioperative and Critical Care: endorsed by the American College of Emergency Physicians and the Society for Academic Emergency Medicine." Circulation 116(16): 1855-1863.

[168] FDA Guidance 2013 *op.cit.*

These descriptions are similar to the aim of public disclosures (see Section 2.4, Theme 4 above). The direction of communication seems to be one-way: telling the community about the research (explaining, stating, making communities aware), and being transparent about what will happen. There is much less focus on two-way communication, consulting them about what ought to happen. Even giving the community an opportunity to express their views does not seem to view them as deciders or part of the decision-making, even though this has been proposed by some commentators[169,170,171]. The FDA guidance underlines this point. Firstly, the guidance says the IRB should check plans for community consultation (and public disclosures) to see whether they are adequate (point 44 p16). This gives IRBs control over the extent to which the community consultation affects their own decision-making. Secondly, it seems that IRB needs to take the results of consultation activities into account in its own review, but that it can override community objections:

> For example, the IRB would document its discussion of issues raised during community consultation activities, particularly discussions of community opposition to, or concern about, the emergency research study. If the IRB approves the study despite the objection of some part(s) of the community, the IRB should also document this, and provide its reason(s) for doing so. Point 50, p20[172]

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[169] Biros, M. H. (2013). "Does Community Consultation Matter?" Academic Emergency Medicine 20(1): 104-105.Biros 2013 Biros is unusual in claiming that CC is specifically: 'a two-way communication', where community concerns are 'heard and considered' prior to a study commencing

[170] Halperin et al. (2007) op. cit. references an empirical study of community consultation and public disclosure efforts by Shah and Sugarman 2003, and claims that only a 'minority of the centers reported using 2-way disclosures with the community…'

[171] Shah, A. N. and J. Sugarman (2003). "Protecting research subjects under the waiver of informed consent for emergency research: experiences with efforts to inform the community." Ann Emerg Med 41(1): 72-78. The authors are more focused on limitations of the impact of two-way communication rather than simply its incidence in their analysis. See especially p76-7.

[172] FDA guidance 2013, *op cit.*

There also seems to be no forum for the IRB and community consultation to resolve potential disagreements. This somewhat limits the meaningful impact of the community consultation on decision-making. Overall, it is unclear how the community consultation requirement is to function: 1) as a third party advisory to regulatory review; or 2) as an authoritative decision-maker whose agreement has more protective impact over future participants.

In this chapter section I have used the emergency research regulations, thematically organised, to enrich and characterise the ethical issues raised by the case studies. Below I discuss one final case to examine the issues related to the community consultation requirement in more detail.

3. Case 5: Polyheme: Final ER case study responds to additional US EFIC Requirements

I place the final case study at this point in the chapter as a response to the additional requirements of disclosures and community consultation (Themes 4 and 5) which are unique to the incoming US EFIC Regulations. Issues arising from these requirements have also been foreshadowed by public criticism of emergency research in the pre-waiver regulation era in cases such as PEG-SOD.

The case, Polyheme®, is a US study of pre-hospital then in-hospital phase randomisation of haemorrhagic shock patients. Patients were randomised during the pre-hospital phase to either an artificial blood product, Polyheme, or saline, and during the in-hospital phase to either Polyheme or blood. The study was profiled in two target articles in the *American Journal of Bioethics*. The first article, by Ken Kipnis et al., objected to a waiver

of consent being approved during the in-hospital randomisation phase. This was on the grounds that blood did not constitute an 'unsatisfactory' treatment option (a condition of the waiver applying), and therefore that randomisation to Polyheme or blood was unethical without consent [173]. Other commentaries suggested failures in adequate oversight led to this issue. These included failures in transparency towards the community during the consultation period, and other responsible bodies such as the IRB and the sponsor[174,175]. The second article, by Karla Holloway, focused on the study's impact on racial and community dynamics, drawing particular attention to how community consultation and public disclosure activities operated[176]. Both target articles and the open peer commentaries which followed show Polyheme's importance as a case study for raising issues about community in the decision-making justification.

Polyheme is an artificial blood product, specifically a haemoglobin-based oxygen carrier (HBOC) derived from human blood. Such products proposed to meet the need for 'a universally compatible, oxygen (O2)-carrying fluid when blood is unavailable'. In 2009, a study in the US reported results of a randomised, controlled, open-label study of Polyheme versus the clinical standard of care. (The standard of care comprised a type of saline in the field, followed by stored red blood cells upon hospital arrival[177].) The study recruited

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[173] Kipnis, K., N. M. King and R. M. Nelson (2006). "An open letter to institutional review boards considering Northfield Laboratories' PolyHeme trial." Am J Bioeth 6(3): 18-21.
[174] Kipnis, K., N. M. King and R. M. Nelson (2006). "Trials and errors: barriers to oversight of research conducted under the emergency research consent waiver." Irb 28(2): 16-19.
[175] Dickert, N. W. and J. Sugarman (2007). "Getting the ethics right regarding research in the emergency setting: lessons from the PolyHeme study." Kennedy Inst Ethics J 17(2): 153-169.
[176] Holloway, K. F. C. (2006). "Accidental communities: Race, emergency medicine, and the problem of PolyHeme (R)." American Journal of Bioethics 6(3): 7-17.
[177] Moore, E. E., F. A. Moore, T. C. Fabian, A. C. Bernard, G. J. Fulda, D. B. Hoyt, T. M. Duane, L. J. Weireter, Jr., G. A. Gomez, M. D. Cipolle, G. H. Rodman, Jr., M. A. Malangoni, G. A. Hides, L. A. Omert and S. A. Gould (2009). "Human polymerized hemoglobin for the treatment of hemorrhagic shock when blood is unavailable: the USA multicenter trial." J Am Coll Surg 208(1): 1-13.

trauma patients in haemorrhagic shock (where blood loss means the heart can longer pump sufficient blood around the body). The title of its index scientific paper, 'Human Polymerized Hemoglobin for the Treatment of Hemorrhagic Shock when Blood Is Unavailable', belied a complex set of ethical issues which ultimately led to the demise of Polyheme's manufacturer and Research Sponsor, Northfield Laboratories, Inc.. In the same year this paper was published the company applied to liquidate its assets after the FDA disallowed further human testing of a modified version of Polyheme[178].

Two main issues arise about how the community consultation functioned in the Polyheme study (which I will refer to simply as 'Polyheme' henceforth). Firstly, the extent to which it was consultative and impacted the decision-making of researchers and the IRB. Secondly, what fulfilling the requirement revealed about the historical and cultural context of the research. Polyheme also connects to Theme 4 (Disclosures), both in the way the consultation requirement overlapped with the public disclosure requirement, and in the way internal disclosures within the research establishment were managed.

3.1. Issue 1: the extent to which community consultation was consultative

The first issue is raised by limitations on the extent to which the community consultation (CC) in Polyheme was consultative. Kipnis et al. provide a thorough analysis of this issue, suggesting a 'dysfunctional system' of regulatory oversight hampered operation of both decision-making bodies within the research establishment, and the CC itself[179,180].

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[178] Reuters. June 2, 2009. Northfield Laboratories to liquidate under Chapter 11 https://www.reuters.com/article/northfieldlaboratories/northfield-laboratories-to-liquidate-under-chapter-11-idUSBNG20947820090602 Accessed 26 May 2019
[179] Kipnis et al. (2006) Barriers *op. cit*.
[180] Holloway (2006) *op.cit.*

This view is supported by Dickert and Sugarman, who claim the study Sponsor withheld information, such as key safety data about Polyheme derived from an earlier phase study, from the CC[181]. The data revealed a 'statistically significant increase in serious adverse events in [aortic aneurysm] patients treated with PolyHeme'. Dickert and Sugarman imply withholding the information may have actively misrepresented the study to the community, with the community 'even assured that PolyHeme had been associated with "no clinically relevant adverse effects"' p162. Interestingly these data were presented to the FDA as part of a separate regulatory approval, and the adverse events were attributed to causes other than the study drug. The implication from this is that while the FDA may have accepted that adverse events were unrelated, it is unknown whether the community or potential participants would have reached the same judgement. This points to different valuing of safety data and risk by those outside the research establishment (such as the community, and participants). Dickert and Sugarman go on to make a subtle point about what constitutes adequate informing of the CC. This is in the context of the Sponsor arguing that it was necessary to withhold safety data and the study protocol because of proprietary privilege. The authors say that both in the case of participants in a normal consent study and in the case of conducting CCs, parties should be given 'crucial information' and 'information material to their evaluation' i.e. relevant information to make an informed decision. However, they resist the idea (from Kipnis et al.) that the CC has a claim to information possessed by internal actors:

> We are not convinced that the claims of community consultants differ in scope or content from individual participants' claims to information in other studies. p163

[181] Dickert and Sugarman 2007 *op.cit.*

Aligning the informational claims of participants with the CC suggests the CC functions as something of a consent substitute. It also suggests the CC is conceived as being external to internal actors deciding about the research (e.g. the IRB, the data monitoring committee, other regulators such as the FDA). This is something which Kipnis et al. also note. They describe that prior decision-making by the clinical trials regulator, the FDA, to approve the study was said to lock the FDA and Sponsor into 'an agreed-upon study design', after which neither IRB nor CC judgements could have been taken into account[182]. For Kipnis et al., not including the CC within decision-making is a barrier to effective study oversight. Dickert and Sugarman are less certain, however. They do not think the CC should be so included with special access to study information which would level informational asymmetries between them and internal actors. Yet at the same time they say 'allegations of withholding information' from the CC are damaging to public trust. They seem to suggest that avoiding such allegations involves clarifying there is no special claim to information, rather than improving CC access to information. However, even on this modified conception of the CC, it may still usefully serve transparency goals, so helping to legitimate emergency research:

> Although community consultation serves other goals in addition to transparency, promoting transparency is absolutely one of the essential ways that community consultation can help to legitimate RES [(research in emergency settings)] conducted under the exception from the requirement to obtain consent (Silbergleit 2007). p163

[182] Kipnis et al. (2006) Barriers *op.cit*. p18.

It is uncertain whether Dickert and Sugarman's arguments here are coherent. Being effectively transparent through the CC is at odds with withholding information from it, especially information likely to harm the case for the research. Part of the problem here may be lumping the conception of disclosure with consultation. On a strict conception of disclosure as one-way communication without a decision-making impact, recipients of information may not contest the research or the basis of its decision-making, e.g. how safety data was interpreted. On a strict conception of consultation as two-way communication with a decision-making impact, the community may contest decision-making and its views should be taken into account. The question is then about what extent of impact the CC should have. Richardson et al. give a view on this:

> Consultation involves solicitation of advice and information; it is not a request for approval or permission. p33[183]

Yet if the CC objects to a study in its current form (remembering that the FDA guidance speaks of the IRB approving research despite community objection), this seems to be a type of disapproval or lack of permission. The lack of clarity is over how, and to what extent, an objection should impact decision-making at regulatory review. By distinguishing the functions within conceptions of disclosures and the CC, it seems we should not understand CC as simply achieving transparency in the manner of disclosures. It is also positioned in the process as potentially critical of the research. This would make it part of authoritative decision-making in its own right at regulatory review. Through this, if aware of the basis for

[183] Richardson, L. D., R. Rhodes, D. F. Ragin and I. Wilets (2006). "The role of community consultation in the ethical conduct of research without consent." Am J Bioeth 6(3): 33-35; discussion W46-50.

regulatory review decisions, CC may also criticise decision-making itself. This might differentiate it from decision-making at regulatory review. Rather than being simply a contributor to regulatory review or endorser, it might also hold others' decision-making to account.

A further way in which this case speaks to Theme 4 (Disclosures) is by insufficient transparency between researchers and decision-making bodies within the research establishment. Kipnis reports that in the case of IRBs which disallowed the study at particular sites, their principal investigators failed to report this to the Sponsor (Northfield). Similarly, according to Kipnis, some sites withdrew applications for ethical approval if it seemed likely that the IRB would disallow the study[184]. Its internal decision-making culture was avoidant of transparency and 'gamed' the oversight system. This risks undermining the authority of different decision-making bodies, and trust in decision-making.

3.2. Issue 2: historical and cultural context

The second issue relates to what fulfilling the CC requirement revealed about the historical and cultural context of the research, and ethical implications. Holloway's article explores this issue which also overlaps with Issue 1 questions above about the extent to which CC was consultative. Her article suggests the concept of community, and the community consultation requirement, is a convenient way to disengage from more complicated problems about social inequality in the US, including the right of African-American communities to be regarded as individuals who possess individual self-determination[185]. In this way emergency research, which cannot regard the individual and

[184] Kipnis et al. (2006) Barriers *op.cit.*
[185] Holloway (2006) *op. cit.*

has instituted a community consultation requirement, is reinforcing socially unequal treatment of African-Americans, and other marginalised groups. This also recalls the abuses of research participants from marginalised groups in recent history[186].

She describes a similar example of authority conflicts between decision-making bodies at one Polyheme study site in North Carolina, US. In this example, bodies extend further than the research establishment into those representing the state. While the Duke University Medical Center IRB approved the study with a consent exception, this conflicted with a state patient's bill of rights which did not allow research without consent. Yet eventually via pressure from local research centres the bill was amended to allow for waivers. Holloway implies these centres were in some way supported by a 'federal authority'. In as far as the patient bill or the various boards or commissions represent the state and thus public and community interests in the study, Holloway uses its amendment to pit the research establishment against community interests[187].

Holloway also notes the efforts to consult African-American communities in North Carolina 'seemed perfunctory… Some indication of [the study's] standing within the black community is evident in the rebuff it received when requesting to speak to the congregations of two black churches in Durham regarding the proposed trial.' By rejecting the study, the community could claim they objected to it. However, researchers could claim that since the CC did not occur, there was no objection or endorsement of the research. In Holloway's view the requirement is not geared to be sufficiently sensitive to contextual

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[186] Jones JH. (2008). "The Tuskegee Syphilis Experiment," in Emanuel, E. J., R. A. Crouch, C. C. Grady, R. K. Lie, F. G. Miller and D. D. Wendler (2008). The Oxford Textbook of Clinical Research Ethics. Cary, UNITED STATES, Oxford University Press, Incorporated. p86-96
[187] Holloway (2006) *op. cit.*

factors of race, history or society. Why would Durham rebuff the research? Holloway suggests an answer:

> Given its [the community of Durham's] history of segregated medical care and the distrust and misunderstanding that have extended from those days, there seemed a missed opportunity for Duke to develop a community consultation process that engaged more rigorously with urban Durham. p14

However, *pace* Holloway and indications in other accounts[188, 189], there are few comprehensive accounts arguing for CC because it sensitizes the research to community context. Richardson et al. do explore this, characterising the CC as contributing to the design and conduct of the research:

> Consultation with the community may reveal information about risks to participants that were not previously identified…[and] may provide suggestions about ways to improve the study by incorporating needed services or educational resources into the research protocol… p34

It is possible to discern a difference of emphasis between Holloway and Richardson et al. The former sees context sensitization as justified irrespective of outcome. The latter sees it as more instrumental to the outcome of more successful research. This emphasizes questions about the CC's authority and function within decision-making. It is unclear whether we should take CC to be: 1) a decider and authoriser about which research proceeds, and so part of regulatory review or its critical friend; or 2) an endorser of regulatory review decision-making, and so a third party advisory to decision-making at regulatory review with less authority; or 3) a proxy group consultee which advises on the

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[188] Richardson et al., 2006, op cit

[189] Dickert, N. W. and J. Sugarman (2007). "Getting the ethics right regarding research in the emergency setting: lessons from the PolyHeme study." Kennedy Inst Ethics J 17(2): 153-169. p164. In their conclusion authors call for 'context sensitive' consultation.

willingness of future participants to be enrolled in the research. This third consultee function is still advisory to regulatory review, but is concerned with decision-making about permissible participant enrolment rather than permissibility of the research *per se*. The CC would thus function informally to advise and endorse the future enrolment of a group of participants. Although not acquainted with the group or acting as its legal proxy, the CC's qualification to offer advice or endorsement would seem due to its relationship to the group as part of the same community. In addition, given information about individual participants would not be available, the CC might instead base its advice and endorsement on grouped characteristics of the participant cohort (the medical condition of interest, likelihood of mental incapacity, potential for benefit of experimental therapeutics). Such characteristics would be used by the REC or IRB for decision-making at regulatory review. However, in also being considered by the CC, we could claim these characteristics would be calibrated to community norms, and situated contextually within a community's sense of what is acceptable for its members. In this way the CC would offer a more nuanced appreciation of whether the participant cohort is permissibly enrolled in future. Nevertheless, this third consultee function would still carry unclear authority with respect to decision-making at enrolment, where authorisation would normally be required[190]. Were the CC to claim legitimate authority to endorse or approve future enrolment, this would further the sense (from Section 2.1 above) that individual level decision-making at enrolment itself is superfluous[191].

[190] This is thinking of normal consent as an autonomous authorisation, as I discuss in Chapter 1, Section 5.2.
[191] In Chapter 5 I argue for the value of role of the physician-researcher in decision-making at the level of individual participant enrolment. However, I acknowledge that the CC may help the physician-researcher to rehearse her role in advance of her actual decision-making.

Polyheme illustrates there is a lack of conceptual clarity over the function and authority of CC. Nevertheless, the CC appears to be helpful in sensitizing both researchers and the community to ethical issues relevant to the research. The community sensitizes researchers to cultural and historical issues which are relevant to how the research should proceed in the local context. The researchers sensitize the community to information about the research and its planned participant cohort. Polyheme also shows the need to differentiate between the conceptions of the CC and public disclosures, and describes some challenges for disclosures between internal actors within the research establishment.

4. Chapter conclusion

In this chapter, I developed the five themes arising from Chapter 2 using a conceptual analysis approach. In doing this, I established a focus within the thesis on justifying decision-making based on the requirements of US EFIC Regulations. These regulations are the more demanding set among the regulations described, and so represent the more demanding justification challenge to address within the thesis. They are unique in having located new ethical issues within the environs of the community, the public and the research establishment, by requiring external and internal disclosures about the research and community consultation prior to the research's regulatory approval.

A chief finding in this chapter is represented by Themes 1 and 2. This is a strategy I derived from the regulations to reconcile permitting exceptions to the rule of normal consent, while retaining the rule of consent where possible. The strategy depends on being able to harmonise two areas of decision-making (shown in Table 1 below): 1) decision-making at the general level during regulatory review; and 2) decision-making at the individual level of each participant's enrolment which ensures the waiver is permissible.

However, it appears that presumptions of waiver permissibility at the general level may be influencing or side-lining decision-making at the individual level. This thwarts the strategy since only at enrolment can we ensure that the waiver is actually permissible, i.e. that neither the specific patient nor his proxy is capable of consent. This is illustrated by concluding conceptual Figure 1 below.

The community consultation requirement (Theme 5) plays an unclear role in decision-making, although through Case study 5 (Polyheme) I have shown that it raises issues relevant to the historical and cultural context of the research. From descriptions in this chapter, it may be an external third party advisory to regulatory review. However, I shall look at its role in detail in Chapter 4. Over the next two chapters (Chapters 4 and 5) I will justify each decision-making area (the general and the individual) in turn, also proposing how they should harmonize and interact productively.

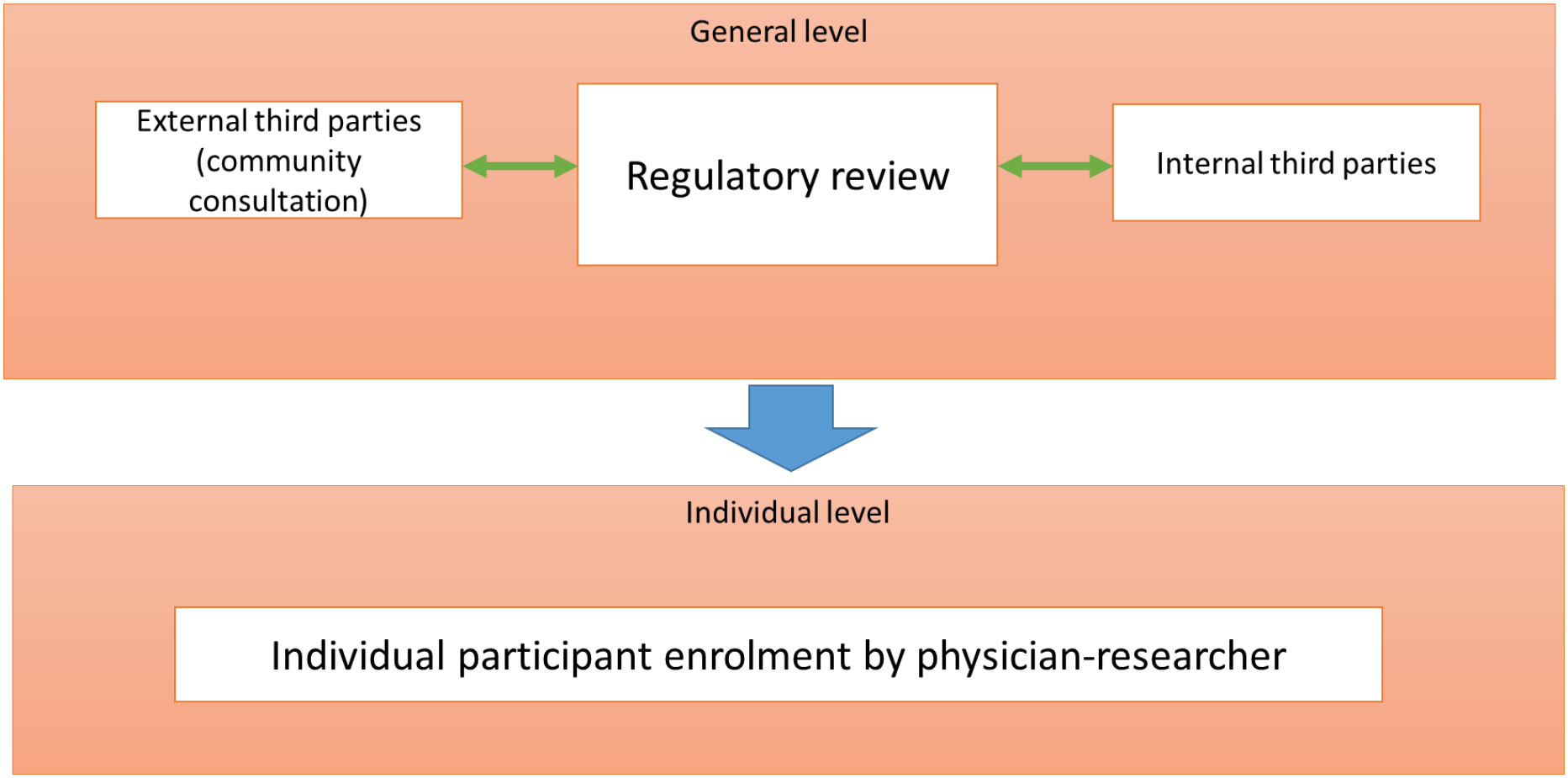
4.1. Table 1: areas of decision-making in emergency research

	Area and focus of decision-making	Ultimate decision	Environment of decision-making	Parties involved
1	Area: at the general level of regulatory review, such as ethics review Focus: the general profile of the research and participant cohort which will be enrolled.	Approval of the research on the presumption that waiver will apply in most or all enrolment cases	Prior to the research commencing. Time-rich environment	- Predominately the IRB or REC which conducts regulatory review. - Taking internal third party advice within research establishment[192] - Taking external third party?[193] advice outside the research establishment from the community consultation
2	Area: at the individual level of participant enrolment with a waiver of consent Focus: the specific participant eligible for enrolment.	Enrolment of each participant upon ensuring the waiver applies in his specific case.	During the emergency phase of the research, at enrolment of each emergency patient to the research. Time-pressured environment.	The physician-researcher as one individual, or multiple individuals reflecting the dualism of care-research duties in therapeutic research.

[192] by 'research establishment' I mean those with professional stakes in the research such as researchers, IRBs, Sponsors, commercial partners, or consultants such as lawyers

[193] In the next chapter (Chapter 4: justifying emergency research decision-making at regulatory review), I resolve questions of the function, authority and positioning of the community consultation with respect to regulatory review.

4.2. Figure 1: influence of general- over individual-level decision-making area



In this Figure, double green arrows represent taking advice from third parties with the opportunity for two-way influence and communication. The single blue arrow represents potential one-way influence of general- over specific-level decision-making.

Chapter 4: Justifying emergency research decision-making at regulatory review

1. Introduction

In this Chapter, I examine what justifies emergency research (ER) decision-making at the general level of regulatory review, leading to the research's approval. First I distinguish the ethics of ER decision-making from the ethics of ER. Then, I use relevant accounts in the literature to analyse reasons which are given for decision-making at regulatory review of ER. As part of analysis, I critique each account, in order to clarify its internal coherence, and the extent to which I can reasonably relate it to my justification question in the chapter. In Section 4, I go on to discuss 'missing reasons' from the accounts, namely an absence of focus in the accounts on the community consultation requirement and reasons for this. In response, I propose the consultation requirement may be useful as an acknowledgement and assessment of social injustice in relevant cases. I then give my own justification for decision-making at regulatory review, and say how the justification aligns with decision-making themes developed in Chapters 2 and 3. I close with how the justification argues for changes to regulations and associated policy guidance.

2. How I understand and use justification in this chapter

In Chapter 1 I established how I understand justification as the type of argument, and how I use it to make arguments in the thesis (see also Chapter 1 Section 7). I defined justification as an argument which defends sufficient and coherent reasons for non-ideal, real-world practice, without requiring actual agreement or acceptance of those reasons. I contrasted this with legitimacy of reasons, which I took to be an account of

their actual acceptance when they are given. Justification aligns with my approach to analysis (see Chapter 1, Section 8) which operates at a theoretical and conceptual level, and so is not primarily concerned with acceptance of reasons or arguments at the actual, empirical level. This analytical approach allows me to focus on analysing justificatory reasons given by accounts. It also helps me to observe where accounts use empirical components within the justification. I shall examine whether such empirical components support or undercut the justification given. Supportive components are candidates for inclusion in my own concluding justification.

3. Accounts offering reasons for decision-making at regulatory review

As introduced in Chapter 1, by examining reasons for decision-making in this chapter, I make a broad distinction between the ethics of emergency research and the ethics of its decision-making. Broadly speaking, the ethics of emergency research refers to the content of ethical issues in particular instances of research. Through an account of the ethics of research (noting that multiple accounts may be given), analysis encounters questions about the ethics of research decision-making. This broadly refers to the ethics of processes, roles and operations within regulatory review which weigh the ethics of the research. Although this process-content distinction is a useful starting point for distinguishing the ethics of decision-making, this does not mean that reasons for justified decision-making may not share a mixture of procedural and substantive characteristics[194].

[194] See Chapter 1, Section 6, for further discussion of the distinction between the ethics of research and ethics of research decision-making.

There are no published accounts which offer a complete justification for emergency research decision-making at regulatory review. This, combined with a justification for decision-making at enrolment, is the knowledge gap the thesis seeks to fill. By 'complete justification' I mean a justification which sets out to justify emergency research decision-making primarily and completely. Either the current literature examines the ethics of the research primarily, with the ethics of its decision-making largely omitted (see for example Accounts 2 – 3 below). Or it examines a particular aspect or requirement connected to research decision-making, for example, the community consultation requirement, but not the complete set of requirements which reflect decision-making as a whole. In addition, the latter such examinations are mostly designed to address practical regulatory implementation challenges, and so do not engage in extensive conceptual analysis[195,196].

My choice of accounts and analysis of them therefore proceeds by a composite approach. I have chosen accounts below which relate to emergency research decision-making. I then examine reasons within them which are relevant to justification. By 'accounts which relate' I mean accounts which give:

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[195] The body of work by Michelle Biros is an example of this. Biros has published extensively on emergency research regulation, but either with reference to one requirement, or discussing complete requirements but with a view to practical implementation. See, for example, Baren, J. M., J. P. Anicetti, S. Ledesma, M. H. Biros, M. Mahabee-Gittens and R. J. Lewis (1999). "An approach to community consultation prior to initiating an emergency research study incorporating a waiver of informed consent." Acad Emerg Med 6(12): 1210-1215. And Biros, M. H., S. S. Fish and R. J. Lewis (1999). "Implementing the Food and Drug Administration's final rule for waiver of informed consent in certain emergency research circumstances." Acad Emerg Med 6(12): 1272-1282.

[196] Work by Neal Dickert and Jeremy Sugarman uses conceptual analysis but as applied to one aspect of decision-making. See Dickert, N. W. and J. Sugarman (2007). "Getting the ethics right regarding research in the emergency setting: lessons from the PolyHeme study." Kennedy Inst Ethics J 17(2): 153-169. See P156-9 for a discussion of the 'unsatisfactory' criterion.

i) reasons for emergency research itself (rather than its decision-making); or

ii) reasons for general research whose conduct does not depend on consent (and so can apply to research without consent); or

iii) reasons for general research decision-making.

In analysing account types i) and ii), I aim to isolate relevant reasons for the research, and then derive some possible reasons which follow for its decision-making. I take a similar attitude towards the use of frameworks in the accounts. Many of the accounts giving reasons for research rather than its decision-making show how to apply the justification in practice using frameworks. Using frameworks involves judgement about whether and how individual conditions within a framework apply in particular cases. Decisions include the hierarchy and weight to give conditions depending on the particular case[197]. These therefore reflect aspects of the ethics of decision-making.

3.1. Account 1: Faden and colleagues

Ruth Faden and colleagues give the account of the Learning Healthcare System (LHS). This account argues for reform of traditional research ethics, including traditional systems of oversight[198,199,200]. Its main argument is that we have a social obligation to

[197] Faden, R. R., N. E. Kass, S. N. Goodman, P. Pronovost, S. Tunis and T. L. Beauchamp (2013). "An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics." Hastings Cent Rep Spec No: S16-27. See S20 where authors give a similar description of weighting of obligations within their ethics framework.
[198] Faden, R. R., N. E. Kass, S. N. Goodman, P. Pronovost, S. Tunis and T. L. Beauchamp (2013). "An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics." Hastings Cent Rep Spec No: S16-27.
[199] Faden, R. R., T. L. Beauchamp and N. E. Kass (2014). "Informed consent, comparative effectiveness, and learning health care." N Engl J Med 370(8): 766-768.
[200] Kass, N. E., R. R. Faden, S. N. Goodman, P. Pronovost, S. Tunis and T. L. Beauchamp (2013). "The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight." Hastings Cent Rep Spec No: S4-S15.

commit to a common purpose of learning (i.e. research), in order to improve healthcare. This obligation challenges the requirement for normal consent, sometimes lessening the requirement to be opt out or opt in consent approaches, and at other times waiving individual consent altogether, referred to as 'streamlined' consent[201]. As is clear, the account does not relate directly to emergency research, but does relate to the ethics of research without consent. Additionally, the proposed reform of research ethics entails managing a transition from consent as a norm to consent waivers in some cases. Its reasons are therefore relevant to my justification question, and to the overall decision-making strategy which I have proposed in Chapter 3 for reconciling rule exception (waiver of consent) with rule norm (consent).

In the first part of the account, the authors justify the move from traditional research ethics to a LHS. The LHS has a commitment to learning and improvement, secured by three goals: 1) a just healthcare system, a societal goal; 2) high-quality care, via efficient and real-time learning; and 3) economic well-being, via efficient learning. These justice-driven goals contrast with a traditional focus in research ethics on protection from risk, abuse and unjust distributions of research burdens. They argue for the move in focus from protection to justice in healthcare so that people can access adequate and affordable care.

A focus away from protection has implications for research ethics. Specifically, it will address a problem of burdensome regulation for research, which slows its progress and the seamless integration of its results into clinical practice[202]. They also take issue with

[201] Faden et al. (2014) *op.cit.*
[202] Kass et al. (2013) *op.cit.*

the moral relevance of common ways in which we distinguish between research ethics and clinical ethics – for example, the assumption that research necessarily confers more risks than equivalent clinical practice[203]. Instead we should refocus 'central moral concerns'[204] to achieve a continually improving system of care, appropriately but not excessively regulated. This would address gaps in the evidence base for care, and relieve some 'learning activities' of disproportionate oversight burdens, what they call problems of under-protection and over-protection respectively.

Then the authors define a learning activity. This activity both delivers healthcare or uses health information, and has a targeted learning objective. Such activities include 'clinical research, clinical trials, comparative effectiveness research, quality improvement research, quality improvement practice, patient safety practice, health care operations, quality assurance, or evidence-based management'[205]. (In comparison with emergency research, the activities here stop short of clinical trials of investigational medicinal products or devices.) The authors propose to identify and justify such activities under an ethics framework. This comprises seven elements, phrased as independent ethical obligations, to justify activities. The framework with each obligation, the parties bearing it, and its method of securement is laid out in the table below (adapted from Table 1 in the paper).

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[203] Kass (2013) *op.cit.* S10 'it remains unclear that evidence exists regarding which enterprise – clinical practice or clinical research – imposes the higher level of burdens and risks on patients beyond those associated with sound clinical management'.
[204] Kass et al. (2013) *op.cit* S12
[205] Faden, R. R., N. E. Kass, S. N. Goodman, P. Pronovost, S. Tunis and T. L. Beauchamp (2013). "An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics." Hastings Cent Rep Spec No: S16-27. S19

Table 1 Faden and colleagues: LHS ethics framework (adapted)

Obligation	**Parties bearing the obligation**	**Method of securing the obligation**
1 respect the rights and dignity of patients	All (researchers, clinicians, health care systems administrators, payers, purchasers)	- Assess impact of the learning activity (LA) on rights, respect and dignity of patients. - Assess whether the LA limits patient choice
2 respect clinician judgements	All but clinicians	Assess impact of LA on clinician judgement, including restricting judgement
3 provide optimal clinical care to each patient	All, unless researchers are not also patient's clinicians[206]	Assess expected net clinical benefit for patients affected by the LA, compared to their net clinical benefit were their clinical care not affected by the LA
4 avoid imposing nonclinical risks and burdens on patients	All	Assess nonclinical risks to patients affected by the LA, compared to their nonclinical risks were they not affected by the LA
5 address health inequalities	All	Assess disproportionate burdens or benefits on already disadvantaged or advantaged patients, assess reduction in inequalities from activities
6 Conduct continuous learning that improves quality of clinical care and health care systems	All	Commit to the LHS, assess impact of an activity to the LHS
7 Contribute to the common purpose of improving the quality and value of clinical care and health care systems	Patients	- Participate in activities in the LHS without express consent, given other respect-intending obligations are in play - Consider participation in other activities where we should get consent

[206] The footnote clarifying this states: 'If researchers do not otherwise have clinical duties to the patients who are affected by a learning activity, then they do not shoulder an obligation to provide patients with optimal clinical care.'

Each obligation is thought to be necessary for 'an adequate ethics' but not sufficient. They are not 'morally weighted or placed in' a hierarchy since specific contexts will determine weight and priority. Each obligation is secured by a mixture of assessing its impact or benefit, or positive stakeholder commitments to the obligation in the case of Obligations 6 and 7.

Obligations 1 to 4 reflect and merge some established research (1 and 4) and clinical (2 and 3) ethics principles, for example avoiding nonclinical burdens and respecting clinical judgements. Obligations 5-7 are new additions. Among these, certain obligations alter requirements for consent, pursuing novel goals of quality, value and just healthcare. Obligation 1 is said to incorporate respect for patient autonomy, but without giving it 'undue deference or overriding importance'[207]. The novel obligation 7 further moderates respect for autonomy in obligation 1 (consent) by committing patients to a common purpose of learning without express consent in some cases. In order to justify this, the authors draw on a Rawlsian principle of the common good[208]. Faden et al. develop this principle into a norm of 'common purpose' which secures common interests by supporting the just institution of the LHS. This is 'a shared social purpose that we cannot as individuals achieve' (S23). It requires agreement at a broad societal level in order to achieve LHS goals (just, quality, and economically beneficial healthcare). The authors then clarify the strength of obligation 7 in practice. They do not see it as an 'affirmative moral obligation' to participate in every learning activity without consent,

[207] Faden et al. (2013) *op.cit* S20
[208] Rawls, J. (1971). A Theory of Justice. Cambridge, Mass, Harvard University Press.p246. Rawls says this can be invoked to defend compliance with situations of 'less extensive liberty', such as regulating 'liberty of conscience and freedom of thought' in order to maintain public order within institutions

since different activities will affect rights and interests to differing extents. They stratify the strength of the obligation using examples of high and low risk activity. Participation in high risk activity is not obligatory. However, participation in low risk activity, for example in 'reviews of deidentified medical records', may be obligatory.

Obligation 7 is compatible with System obligations to 'inform patients about learning activities and solicit [patients'] express consent for some learning activities, as appropriate' (S24). Later such obligations are phrased as disclosures which 'underscore to patients the system's moral commitment to …learning, the relationship of that learning to the quality of care they will receive, and … to ensuring that patients are aware of continuing learning activities and their risks and benefits' (S25). This is described as creating a 'moral link' between obligations 1 and 7 which illustrates how patients pursue the 'common purpose' of the system, sometimes at the expense of their express consent. Making the link in practice might include 'information provided at initial interviews or at enrolment, in postings, in waiting rooms, and in newsletters and Web sites' (S25). Obligation 7 also extends to proxies of incapacitated patients whose information can also contribute to learning.

Obligation 5 is also novel and emphasises a broader role for justice in LHS activities than has been previously described in traditional research ethics. This is 'an affirmative obligation to direct learning activities toward aggressive efforts to reduce or eliminate unfair or unacceptable inequalities in the evidence base available for clinical decision-making, in health care outcomes, and in the respectfulness with which health care is delivered' (S22). This obligation aims to even out distribution of risks and benefits

arising from the LHS's activities between 'already socially and economically advantaged' and already disadvantaged patient groups.

Criticisms of Account 1

In this subsection, and other 'Criticisms' subsections of the accounts which follow, I critique each account. This is in order to clarify its internal coherence, and the extent to which I can reasonably relate it to my justification question in the chapter.

Account 1 (Faden) promotes a radical transformation of traditional systems of clinical and research ethics into a hybrid system. There are ways in which this reflects the emergency research strategy to reconcile a rule norm in the regulatory model of research ethics (normal consent) with a novel rule exception of the consent waiver[209]. For example, the LHS combines standards from traditional systems (obligations 1-4) with novel standards for a novel system (obligations 5-7) within its Framework. However, Faden is arguing for complete 'transformation' from traditional to novel systems of ethics, moving from a protectionist to a just system, not for a way in which aspects of old and new systems can reconcile. Yet in the emergency research case, it may be necessary to retain aspects of existing protectionist systems, particularly as some emergency research (for example trials of novel therapeutics or devices) is more risky than learning activities under the LHS. LHS activity, even when more experimentally leaning, yet relies on delivering adequate care since this is overall orientation of the LHS. As such, even though the account's definition of a learning activity above includes clinical trials, these are not envisaged to be trials of novel therapeutics or devices, but

[209] See Chapter 3, Section 2.1 for details of this strategy.

only those with an existing profile of use in clinical practice. This gives reason for emergency research to maintain the foundational status of consent as part of the regulatory model of research ethics in some cases. In contrast, Account 1 may more reasonably 'move on' to the justice-based approach where consent's status is less foundational.

Account 1's main argument, social obligation to commit to the common purpose of the LHS (without express consent in some cases), is conceptualised as a theoretical agreement. It is a moral commitment to 'a shared social purpose that we cannot as individuals achieve' (S23). The argument thus takes its force from its theoretical nature, and does not require real-world agreement to be justified. Yet, in sections which discuss how to manage framework obligations reflecting the common purpose (obligations 1 and 7), concrete information-giving and disclosures are required. This suggests the justification requires regular, public iterations of the commitment made (our actual agreement) to the common purpose. However, as a justification, the argument holds irrespective of reiterating the commitment we should make, were we asked. In which case, the account should clarify that disclosures are supportive empirical components of the justification. The LHS framework which implements the account's arguments may play a dynamic role here in emphasizing empirical components, since its task is to make the argument meaningful at the real world level (see also Section 5 below).

In summary, Account 1 is important for seeing the potential of a model of research ethics without consent as a rule. However, it can be permissibly more demanding than emergency research on patients and society in requiring their obligation to commit to its social purpose of learning without express consent. This is because risks of activities

within the LHS have a lower range of risk magnitude and a lower likelihood of harm, because of an overall orientation in the System to provide adequate healthcare. For higher risk studies in the LHS, consent is required and may still be obtained, given the absence of emergency context.

3.2.Account 2: Largent and colleagues

Account 2 is by Emily Largent and colleagues who propose a 'Consent Substitute Model' to justify emergency research 'without initial consent'[210]. The main argument in the account claims that if we are justified in treating the emergency care patient without consent (based on compelling reason to think he would consent to this), so we may also recruit patients to emergency research under the waiver, provided we can sufficiently align research with emergency care. I use this account because its argument relates directly to emergency research ethics, and relies on a level of general presumption about individual participants' choices and interests. This may therefore yield reasons relevant to my justification question, since at least some emergency research decision-making practices operate on a presumption that the waiver is permissible (see also Chapter 3, Section 2.1, Theme 1).

Largent et al. say 'a clear tension exists between the social value of the knowledge sought and individuals' right to control what happens to them by giving informed consent.' Waiving consent to emergency research has been described as a triumph of the interests of professional research stakeholders over 'the therapeutic interests of present patient subjects'. The account is therefore motivated to show how therapeutic

[210] Largent, E. A., D. Wendler, E. Emanuel and F. G. Miller (2010). "Is emergency research without initial consent justified?: the consent substitute model." Arch Intern Med 170(8): 668-674.

interests or interests in the emergency care situation are reasonably secured in the research (absent consent). It does this by first saying how those interests are secured in emergency care without consent. In doing this, it takes consent to secure both respect for autonomy and protection of individuals' wellbeing. However, in emergencies, it notes that an individual loses autonomy or 'control' over what happens to him and cannot look to his own well-being since he is incapacitated. Even so, it may be still be possible to secure his interests, and to an extent predict the choices he would make. This is because the emergency context makes his basic preferences and interests predictable:

> In emergency situations… there is a substantive, even if not universal, convergence of interests. In an emergency, diverse conceptions of wellbeing typically compress to survival and preservation of mental and physical function p670.

In context, they claim that: a) the range of control, or number of choices over what happens to someone is narrower or 'compressed'; and b) this leads to less range or more convergence in individual ideas of choice and well-being. This convergence is said to meet a 'reasonable person standard' for what constitutes advancing personal interests and well-being in an emergency care context. The standard aims to capture what any reasonable person would regard as advancing their well-being in a medical emergency, not the standards of 'the particular individual'[211]. This standard is 'compelling reason to believe that this person, if able to do so, would consent to the medical intervention'. It

[211] Faden, R. R., T. L. Beauchamp and N. M. P. King (1986). A history and theory of informed consent. New York, Oxford University Press. p36: 'Consent to treatment is often said to be 'implied' in an emergency, but this 'implication' is based on a standard of the reasonable person, not the particular individual'

is reiterated, in the presence of medical need being met and a favourable risk-benefit ratio, as what 'there is no reason to think that the individual would object [to,] based on personal values or interests' p670[212]. Largent et al. stress that this standard is not a 'presumed consent' for clinicians to intervene, but a way of 'not ignor[ing]' patient well-being and autonomy. Having elaborated the reasonable person standard, they claim emergency care without consent is justified.

Second, and building from this first care-oriented argument, the account deals with how emergency research without consent is justified. They argue that it is possible to transfer the reasonable person standard from care to research, so long as research is equivalent to care in certain respects:

> If an emergency research trial evaluating an experimental treatment is sufficiently analogous to emergency medical care for a particular incapacitated individual, enrollment of that individual in the trial is justified.

This leads to the 'Consent substitute model' itself comprising five conditions to ensure equivalence between standard care and the research, and so apply the reasonable person standard to research. The framework, reproduced below, is divided into conditions which establish: 1) therapeutic risk-benefit ratios comparable with care; 2) nontherapeutic minimal risk; and 3) absence of objections to the research. In particular the third condition of 'No conflicting preferences' seems a direct check of the reasonable person standard. It checks that there is no compelling reason to think research conflicts with patient values or interests.

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[212] Largent, E. A., D. Wendler, E. Emanuel and F. G. Miller (2010). "Is emergency research without initial consent justified?: the consent substitute model." Arch Intern Med 170(8): 668-674.

Table 2 Largent and colleagues: framework for securing the justification proposed

Table 1. 5 Conditions for Ethical Emergency Research Without Initial Consent

Condition	Description
Responsiveness	The experimental intervention must be responsive to an urgent medical need of patients.
Comparable risk-benefit ratio	The risk-benefit ratio of the experimental intervention must, in light of the available evidence, be judged favorable, and at least as favorable as the established standard of care and the control intervention, if any.
No conflicting preferences	There should be no compelling reason to think that the experimental intervention conflicts with patients' values or interests.
Minimal net risk	Cumulatively, necessary nonbeneficial procedures should pose no greater than minimal risk.
Prompt consent	Consent for ongoing emergency research interventions and additional interventions should be obtained as soon as possible.

The 'No conflicting preferences' condition also reflects clinical practice checks which are made in order to respect cultural preferences, such as blood transfusion refusal by Jehovah's witnesses. In emergency research, the account suggests community consultation could support such checks, e.g. by providing opt-out bracelets in order to show preferences:

> Community consultation by the researchers can help assure that exclusion criteria reflect predictable personal values and that potential patients are aware of opt-out mechanisms p671.

Other objections to continuing in the research are solicited by the fifth condition of 'Prompt consent'. The account envisages using prepared consent or proxy consent forms (required by the US EFIC Regulations) for securing 'ongoing consent' for participation after the emergency phase of the research. This is even though such forms are prepared in case they can be used *before* the emergency phase of the research.

Criticisms of Account 2

Account 2 (Largent) is at the outset motivated to show how therapeutic interests in emergency care are reasonably secured in research absent consent. Even though its authors claim they are not 'ignoring' autonomy, this makes an assumption that securing wellbeing and therapeutic interests are generally a sufficient 'substitute' for consent's absence, given the emergency context. This allows the authors to diminish the importance of questions of respect for autonomy. One example of this is their claim that something of respect for autonomy may be restored since the reasonable person standard expresses choices which are converged by the emergency. However, this sidesteps the sense of autonomy as self-determination by the individual. It avoids the moral significance of individuals who are to be enrolled, and disengages with issues about how we appropriately treat them at enrolment to the primary, emergency phase of the research. In this way, the account is not minded to marry presumptions that a waiver is permissible with assurances that the waiver is permissible per participant, even though the regulations require this (see Chapter 3, Section 2.2, Theme 2). The account demonstrates this by only requiring attempts at consent after the emergency phase of the research. This is found in its fifth condition, Prompt consent, whose moral sense is that 'emergency research should not <u>continue</u> without consent if it becomes feasible to obtain consent' p671 (my underline).

Account 2 also uses a model for its argument with fixed conditions for what meets the reasonable person standard. For instance, a reasonable person would permit no more than minimal net risk from nontherapeutic procedures (see minimal net risk condition in Table 2 of this section above). This may make the standard inflexible for reviewing research of varying risk profiles, since it presumes no reasonable person

would accept more than minimal risk. Neither does it allow that countervailing reasons might mitigate the need for minimal risk in certain research cases.

Finally, the account's reasonable person standard (RPS) adds an empirical component to the justification in a manner which is unclear. The third condition in Table 2, No conflicting preferences, checks that the research proposed is reasonable for that particular patient. Namely that it does not conflict with preferences which we can ascertain from his medical history, if available, or community norms. This need for actual checks of what is reasonable seems to be an account of the legitimacy of the RPS. Yet earlier in the account, the RPS is theoretically justified by what we should find reasonable (based on the idea of converged choices and interests in an emergency). What should be reasonable is irrespective of actual agreement or acceptance. The check therefore seems to undercut the justification argument. The authors should clarify whether the RPS justification relies on actual checks, or whether such checks support the RPS, but do minor justificatory work themselves. This would clarify the extent to which underlying arguments rely on actual checks.

In summary, Largent et al. offer a compelling account for how to predict choices and interests, both in the clinical and research emergency setting. Some of the conditions in its consent substitute model are too inflexible to account for a range of research risks. Others need to be clarified for how they support the justificatory basis of the RPS. It may be that the model itself has had a dynamic effect on the RPS such that it develops a reliance on empirical components. If so, the account should acknowledge this. Overall, the account may depend too heavily on predictive presumptions that the waiver of consent is permissible. Even were it to rely on support from empirical components

within the RPS (e.g. the check for objections), this might still constitute an insufficient argument at the individual level to ensure the consent waiver is permissible.

3.3. Account 3: Tigard

The next account, Account 3, is by Daniel Tigard[213]. (I will also discuss this account in Chapter 5, the role of the physician-researcher). The main argument in the account offers a doctrine of double effect to justify the *prima facie* wrong of non-voluntary enrolment to emergency research, by it being the by-product of pursuing therapeutic success. The account is based on the case of a therapeutic hypothermia study for severe exsanguination which has led to cardiac arrest. The account relates directly to emergency research ethics and works hard to prioritise the individual patient, and his individual benefit, above the interests of the research. This functions to address concerns of participant exploitation when consent is not possible. This is important for my justification question, since it could provide ways for decision-making to ensure individual participants are considered appropriately.

The account opens with a description of the case study, the 'Emergency Preservation and Resuscitation for Cardiac Arrest From Trauma (EPR-CAT)' trial. The trial recruits trauma patients who go into cardiac arrest in the Emergency Department due to severe exsanguination (commonly known as 'bleeding out'). Therapeutic hypothermia is used to cool the body and gain extra time to make surgical repairs. This case study is said to be 'justified in practice and in agreement with intuitions expressed by community members seen as potential subjects' p345-6. Yet a philosophical justification for

[213] Tigard, D. (2016). "Emergency Preservation and Resuscitation Trial: A Philosophical Justification for Non-Voluntary Enrollment." Bioethics 30(5): 344-352.

nonvoluntary enrolment to the research is claimed to be lacking. Tigard analyses anti-experimentation work by Hans Jonas, derives a doctrine of double effect, and turns Jonas's views into a pro-experimentation (pro-research) justification.

The doctrine of double-effect is a type of argument which defends what is normally considered morally wrong – e.g. ending a life – by making it a by-product of another good effect. For example, this is seen where a physician gives opioid pain relief to relieve suffering in terminal illness, but as a by-product might hasten a person's death[214]. It is also seen where a surgeon removes a pregnant woman's uterus (so destroying the embryo or foetus) in order to treat a serious disorder such as ectopic pregnancy. The by-product wrong is conceptualised as something which is foreseen but unintended. However, it is not sufficient that the wrong is foreseen. In addition, the doctrine always 'presuppose[s] that some kind of proportionality condition has been satisfied. Traditional formulations of the proportionality condition require that the value of promoting the good end outweigh the disvalue of the harmful side effect.' [215] In emergency research, nonvoluntary enrolment and resulting knowledge advancement are the 'moral wrongs' which, without a counterbalancing good effect, threaten to use or exploit the individual as a mere means for the sake of the research.

Jonas's two main conflicting positions are: 1) that we exploit patients by recruiting them to research, since their illness progressively affects their free will, termed the

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[214] McIntyre, A (2019) "Doctrine of Double Effect", *The Stanford Encyclopedia of Philosophy* (Spring 2019 Edition), Edward N. Zalta (ed.), URL = <https://plato.stanford.edu/archives/spr2019/entries/double-effect/>. Section 6. Whether hastening death is actually is a possibility if the pain relief is administered carefully enough, has been disputed by palliative care experts. Accessed 26 May 2019.
[215] McIntyre A (2019) *op.cit* Section 3. Misinterpretations.

'conscription of the afflicted'; and 2) that experimentation is only permissible if it relates to a patient's illness. On point 1), Jonas notes that 'hopeless' cases (patients without chance of survival) are the least justifiable for recruitment. This is because the more serious the illness, the more free will is affected, so compounding their exploitation.

Tigard proposes that, with slight modifications, these two positions can be resolved by a double-effect justification. To do this, he further specifies Jonas's claimed wrong when applied to emergency research: it is wrong to enrol 'hopeless cases' for whom there is no chance of survival without their consent for the sake of medical knowledge. However, Tigard argues that in the case in question, patients are not hopeless but 'nearly hopeless' cases. This means experimentation increases their chance of survival, so averting a disaster (the patient's death). Tigard supports this reason to enrol with another claim from Jonas, taken from his work on the responsible use of technology (including conducting research experiments). This claim modifies Kant's Categorical Imperative: 'Act so that the effects of your action are compatible with the permanence of genuine human life.'[216] Enrolling the patient should therefore be in order to preserve life. This leads to Tigard's core double-effect argument:

> In the case of a clinical trial for emergency situations where informed consent is impossible to obtain, physicians are morally permitted to pursue the advancement of medical knowledge, but only as a byproduct of pursuing therapeutic success p350[217].

[216] Jonas, H. (1974). Technology and Responsibility: Reflections on the New Tasks of Ethics. Philosophical Essays: From Ancient Creed to Technological Man. Englewood Cliffs, N.J., Prentice-Hall. 3–20, p. 13.
[217] Tigard, D. (2016). op.cit.

We should not enrol emergency patients 'unless the condition is such that no successful interventions are known and participating subjects stand to benefit therapeutically from the trial.' Non-voluntary enrolment to the research, and resulting knowledge advancement, is the necessary wrong to pursue aversion of disaster or therapeutic success, given lack of alternatives in clinical practice. The strength of the doctrine is in keeping the issue of appropriate treatment of individuals at enrolment in the foreground. This is done by making it imperative that researchers and institutions intend benefit first and foremost, rather than knowledge from the research:

> the EPR trial's use of non-voluntary subjects is positively morally permissible to the extent that Dr. Tisherman and the collaborating institutions maintain direct therapeutic benefit to participating subjects as their primary motivating intention. p351

Intent to benefit is conceptualised as a mind-set towards the individual patient which physician-researchers should adopt, particularly when committing the ostensible wrong of nonvoluntary enrolment. Their attitude to patients in the research is part of integer research practice where therapeutic intent and research interests are ordered correctly and balanced sensitively. This is demonstrated most clearly through Tigard's quoting of Jonas's words:

> Non-voluntary subjects must first be patients, and physicians as researchers must remain physicians first and foremost. In Jonas's words, the "gain to knowledge and future therapy is incidental to the bona fide service to the present patient."p350

Although this account does not spend much time on research ethics decision-making or governance, Tigard also gives an indication of how intent is practically governed in the research. He says 'physicians as researchers should be initially and continuously held

accountable by ethical review boards and by public opinion' for emergency research[218]. He regards this as extending the justification for the research beyond 'institutional and public approval on proceeding without consent'.

Criticisms of Account 3

Account 3 (Tigard) recognises that participants may be exploited in the research, unless measures are taken to consider them appropriately. It raises the possibility of a role for the physician who is also a researcher in achieving that appropriate treatment. Yet resting the justification on physician-researcher intent to benefit relies too much on her professional integrity. The account could be strengthened by some accompanying checks and balances upon the physician-researcher which decision-making is in a position to afford.

The account contrasts with Account 2 (Largent) in not requiring fixed standards, such as a threshold of minimal risk, to support securing individual participant benefit. This relies too far on the researcher's intent to benefit alone. Relying on intent alone may be justified in cases such as the account uses, where patients are 'nearly hopeless' cases and any action to avoid their death counts as an intent to benefit. However, it may be harder to justify in cases where intent to benefit is more difficult to determine or assess. This may result in too few substantive constraints in its argument overall, when applied to different sorts of cases. The structure of the main doctrine of double effect argument also depends on conceptions of the wrong and the good being proportionately balanced. However, if the wrong is both nonvoluntary enrolment, and the resulting

[218] Tigard, D. (2016). op.cit. p351

advancements to medical knowledge which benefit future patients, this is out of proportion with the good effect of intending individual therapeutic benefit. In which case, the likelihood and magnitude of individual therapeutic benefit would need to be very high, in order to maintain symmetry of the argument's structure.

In summary, Account 3 is important because it tries to address a concern of patient exploitation in the research, pointing to a role for the physician-researcher. However, this role needs supporting with practical oversight to prevent concerns about exploitation re-emerging. It also needs support from substantive constraints to decision-making on what risks and benefits count as acceptable. The emergency research regulations potentially offer relevant substantive constraints to support the account.

3.4.Account 4: McRae & Weijer

The next account, Account 4, is by Andrew McRae and Charles Weijer[219]. The account is a detailed analysis of how risk arising from research procedures should be described in the regulations and assessed. (See also Chapter 3, Section 2.3 where I describe McRae and Weijer's criticisms of how risk is assessed in the US EFIC Regulations). The main argument in the account says research is justified when we can isolate and minimise risks of harm in the research which are not offset by therapeutic benefits. As with Accounts 1-3, the account relates directly to emergency research, but unlike these it deals directly with the risk-based requirements of the US EFIC Regulations. The reasons which it offers are thus potentially very relevant for my justification, since they relate to a core part of emergency research decision-making itself.

[219] McRae, A. D. and C. Weijer (2002). "Lessons from everyday lives: a moral justification for acute care research." Crit Care Med 30(5): 1146-1151

The authors begin the account by suggesting that emergency research patients require stringent additional protections which are not afforded, at least as far as current US EFIC Regulations provide for acceptable risks. This is because these regulations have eliminated a minimal risk threshold in favour of a requirement that risks should be reasonable. They argue that this means participants are potentially exposed to high risks justified by the severity of their medical condition:

> the more dire a patient's illness or injury, the riskier the nontherapeutic procedures that may be performed on the patient. p1147[220]

In response, they propose the following justification:

> It is ethically legitimate to enroll emergency patients in clinical trials with nontherapeutic components without consent if the additional risks of participation are socially acceptable, that is, if they are minimal risks p1150 *ibid.*

Minimal risks are socially acceptable when they are risks 'that are identical or sufficiently similar to those encountered in the daily lives of all persons' p1150. Importantly, such risks cannot refer to the daily life of a critically ill person since that is not referable to a daily life standard, and leads back to the problematic association between risk and severity of the person's medical condition.

To secure this justification, they propose their risk analysis framework should be adapted for use in emergency research, a framework which, at the time of writing the account, had been recently endorsed by the 2000 US National Bioethics Advisory Commission[221,222]. The framework in question uses a per component analysis approach

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[220] McRae, A.D. & Weijer, C (2002) *op. cit.*
[221] Weijer, C. (2000). "The ethical analysis of risk." J Law Med Ethics 28:344–361.
[222] McRae & Weijer (2002) *op.cit.*

to deciding research risks. Firstly, the approach divides research risks up into therapeutic and nontherapeutic procedure types. Different risk types undergo different risk calculations based on their different moral relevance. Secondly, the risks of therapeutic procedures are calculated as permissible relative to predictable therapeutic benefits, with at minimum net therapeutic benefit being permissible, when benefits offset the risks. This is defended by the principle of beneficence, or securing participant welfare. This calculation is to be made by the IRB, using the concept of clinical equipoise. Clinical equipoise occurs in research 'when the expert medical community is in a state of honest disagreement as to the superiority of each study arm [of a randomized controlled trial]' p1147[223]. In another related publication, clinical equipoise is described as follows:

> [It is] a research-friendly response to the question "When may a physician offer enrolment in a clinical trial to her patient?". It provides that she may do so when the therapeutic procedures in a clinical trial are consistent with competent medical care p571[224].

This consistency judgement, though envisaged here as made by a physician, is practically made by the IRB. Thirdly, the risks of nontherapeutic procedures (e.g. an additional MRI scan, or a blood draw) are calculated in light of the advancement of knowledge they pursue, and capped at a minimal risk threshold. Within this part of the risk calculation, risk minimisation involves absorbing some nontherapeutic procedures back into the therapeutic risk calculation. This is if the procedures are already performed for diagnostic or treatment ('therapeutic') purposes. Minimal risk is also decided by the

[223] McRae & Weijer (2002) *op.cit.*
[224] Weijer, C. and P. B. Miller (2004). "When are research risks reasonable in relation to anticipated benefits?" Nat Med 10(6): 570-573.

IRB, which is seen as a social mechanism to judge 'a socially acceptable level of nontherapeutic research risk' p1150[225]. This is either through lay committee members being on the IRB or the IRB being seen as representing society's view. The minimal risk threshold, when calculated by per component analysis, is said to reflect the vulnerability of emergency participants appropriately[226]. The minimal risk threshold in emergency research is more conservative than the threshold which Weijer argues should apply to other vulnerable research populations such as children. This is because without a proxy decision-maker due to the emergency, emergency research participants are 'relatively more vulnerable than children or incapable adults' p573[227]. The algorithm for the per component analysis approach is laid out below:

[225] McRae & Weijer (2002) *op.cit.*
[226] McRae, A. and C. Weijer (2008). "U.S. Federal Regulations for emergency research: a practical guide and commentary." Acad Emerg Med 15(1): 88-97.
[227] Weijer, C. and P. B. Miller (2004) *op. cit.*

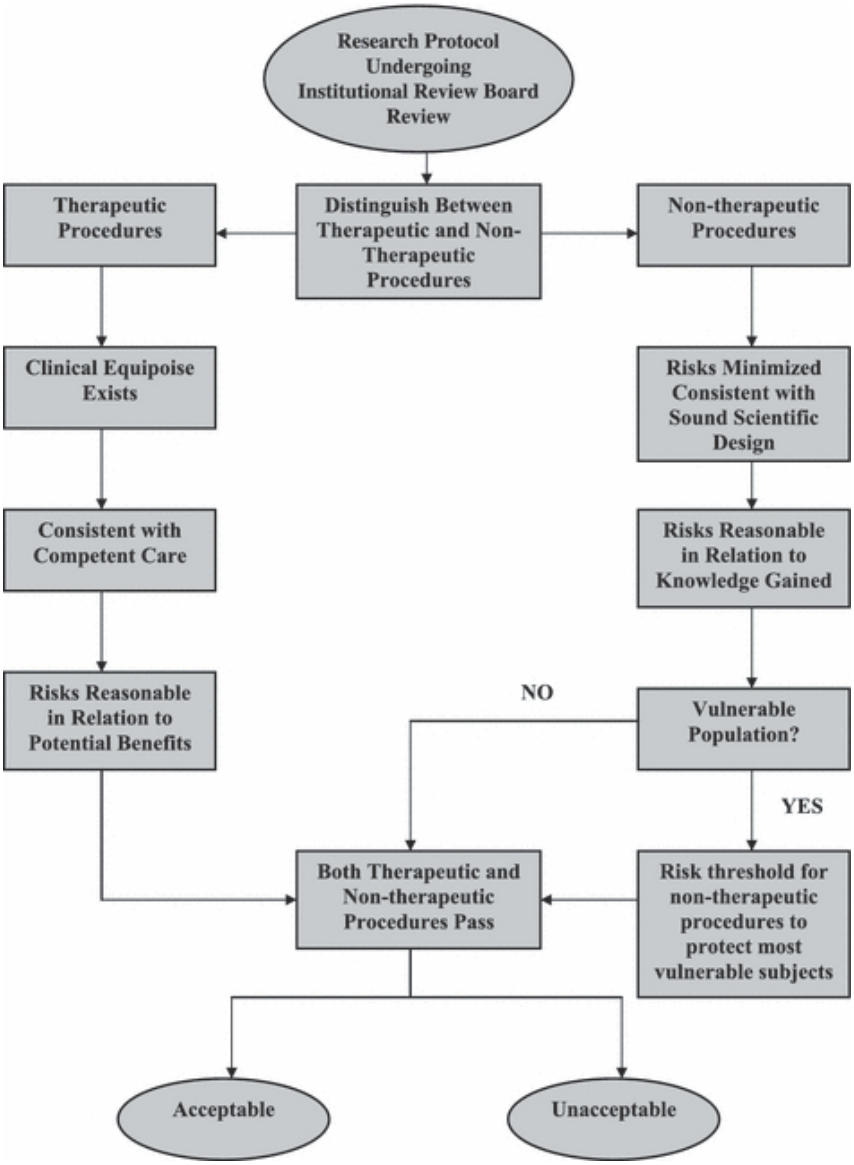


Figure 1: Per component risk analysis algorithm (from McRae & Weijer 2008[228])

As well as reflecting the harm minimisation justification, the authors claim the algorithm is justified by reason of process consistency. In a related publication, they note the algorithm addresses IRB 'inconsistent decision-making', caused by 'vagaries of intuition to interpret federal regulation on acceptable risks and potential benefits'

[228] McRae &Weijer (2008) *op.cit.*

p570[229,230]. They go on to say that 'IRBs and policy makers require a systematic approach to make effective and consistent decisions' and that component analysis achieves this, and is the response to what they call a 'social imperative' for the approach p570[231].

Criticisms of Account 4

Account 4 (McRae & Weijer) agrees with Account 2 (Largent) in proposing a minimal risk standard for nontherapeutic research procedures. A number of issues arise from this standard and how it functions in Account 4's argument.

Firstly, its central argument is unclear about the basis for its underlying claim about risk and society. The argument is that emergency research without consent is permissible provided nontherapeutic research risks are socially acceptable, namely capped at minimal risk. The claims which might underlie this are: 1) minimal risk is what society would find acceptable; or 2) minimal risk is what society should find acceptable. The first claim depends on evidence of society's view about risk and indicates a legitimacy account. On this claim it is not possible to set a general rule about the social acceptability of risk without actual checks of acceptability with society. The second claim depends on setting a general rule about risk: that society should find procedures of minimal risk socially acceptable, irrespective of whether they do find them acceptable. This indicates a justification type of argument. It is also possible that evidential, empirical components function to support a justification type of argument:

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[229] Weijer, C. and P. B. Miller (2004). "When are research risks reasonable in relation to anticipated benefits?" Nat Med 10(6): 570-573.
[230] McRae and Weijer (2008) *op. cit.* See also p95 which suggests that another part of inconsistency arises because of the inconsistency between multiple federal regulations for emergency research
[231] Weijer, C. and P. B. Miller (2004) *op. cit.*

society's views, elicited through the societal mechanism of the REC, legitimate decision-making about risk. In which case the account should clarify that evidencing society's view supports the justificatory basis for regulatory review decision-making. Even with this clarification made, there are residual questions about whether only activities of minimal risk are (or should be) socially acceptable, or whether other activities in addition to those of minimal risk are (or should be) socially acceptable.

Secondly, the cap of minimal risk makes the account inflexible for decision-making. The account bases the need for the cap on participants being especially vulnerable as a group and so deserving of such 'stringent' additional protection[232]. It claims that by applying the cap, regulatory review determines acceptable risk. However, having the cap sets a protectionist tone to the decision-making and so lessens the weight of other relevant, non-risk-based considerations in the discussion. It also limits the scope of risk-based decision-making to accurate comparison of research risks with the 'daily life of all persons' standard. The standard is designed as a universally comprehensible point of reference with minimal risk which avoids interpretation mistakes. However, mandating the point of reference may over-determine how decision-making should conceive of risk in order to make appropriate decisions. Similarly, the step-wise algorithm which should be followed for consistency's sake may over-stipulate decision-making thought processes and so limit flexibility.

[232] This clashes with more recent conceptions of vulnerability as being situation-specific, not predictably applying to entire groups of people. See Luna, F. (2009). "Elucidating the Concept of Vulnerability: Layers Not Labels." International Journal of Feminist Approaches to Bioethics 2(1): 121-139.

Thirdly, regulations' risk descriptions vary in how they define and appreciate risk. This is even the case in the US WIC Regulations which are said to be harmonised with the US EFIC Regulations, but which use a minimal risk threshold where US EFIC does not[233]. For example, the minimal risk threshold of US WIC Regulations refers to the whole of the research, rather than just nontherapeutic procedures. Alternatively, the EU Regulations also have a minimal risk standard but this is calculated in comparison with the subject's standard treatment. Such examples run counter to the approach which Account 4 (and Account 2: Largent) advocates, and result in over-constrictive risk thresholds. A case from the US literature about risk assessments in PhAST (the Prehospital Agitation and Sedation Trial comparing two standards of care) illustrates the complexity which arises where regulations pertaining to the same research jurisdiction vary their risk arrangements[234]. The authors claim that PhAST should not have been approved under the US WIC Regulations, since serious side effects from therapeutic procedures would not have met the minimal risk threshold. Instead the trial should have been considered under the more 'robust process' of the US EFIC Regulations. In their reply, the PhAST triallists maintain the study was approved under the US WIC Regulations because procedures conformed to the standard of care, and so the added research risk was minimal. It seems the triallists therefore incorrectly took therapeutic procedures to be omitted from the minimal risk calculation, while the authors – correctly

[233] Schmidt, T. A., N. M. DeIorio and K. B. McClure (2006). "The Meaning of Community Consultation." The American Journal of Bioethics 6(3): 30-32.This article also notes that the EFIC and WIC Regulations are often confused: 'Technically, a waiver is allowed [under WIC Regulations] in cases for which the research would add minimal risk to the subject.'

[234] Cole, J. B., J. D. Ho and M. H. Biros (2016). "Randomizing Patients without Consent: Waiver vs Exception from Informed Consent." Prehospital and Disaster Medicine 31(4): 457-458.

identifying the more general application of minimal risk in US WIC compared with the US EFIC Regulations – are right to claim they should have been included.

This case raises a further issue about managing risk between sets of regulations. In saying that the US EFIC Regulations offer a more 'robust process' than US WIC Regulations[235], this indicates that US EFIC is a more extensive or burdensome process. As such it may operate as a proxy for determining or managing acceptable risks because it deters studies which cannot meet the minimal risk threshold from applying for regulatory review at all. This, together with claims that IRBs or others are not applying requirements properly, causes a decrease in the number of 'risky' (EFIC-approved) studies overall, so managing the risk of emergency research overall[236,237,238]. Related to this, there is also evidence from the literature that studies are shoe-horning their designs such that they meet the minimal risk threshold of the less demanding US WIC Regulations, even when the design is inferior or substandard to answer the research's objectives[239,240,241]. Therefore it seems having one set of regulations with the minimal

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[235] See Cole et al. (2016) *op.cit.* p457 'Higher risk studies of this nature require "Exception from Informed Consent" (21 CFR 50.24), a far more robust process consisting of five critical elements, including: community consultation; public disclosure before and after the trial; plans for contacting legally authorized representatives to seek consent; formation of a data safety monitoring board; and completion of an Investigational New Drug Application with the US Food and Drug Administration'

[236] Biros, M. H. (2005). "The Ethical Conduct of Resuscitation Research: setting the stage for change." Acad Emerg Med 12(11): 1015-1016.

[237] Hiller, K. M., J. S. Haukoos, K. Heard, J. S. Tashkin and N. A. Paradis (2005). "Impact of the Final Rule on the rate of clinical cardiac arrest research in the United States." Acad Emerg Med 12(11): 1091-1098.

[238] Klein, L., J. Moore and M. Biros (2018). "A 20-year Review: The Use of Exception From Informed Consent and Waiver of Informed Consent in Emergency Research." Acad Emerg Med 25(10): 1169-1177.

[239] Klein, L. R., B. E. Driver, J. R. Miner, M. L. Martel, M. Hessel, J. D. Collins, G. B. Horton, E. Fagerstrom, R. Satpathy and J. B. Cole (2018). "Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation in the Emergency Department." Ann Emerg Med 72(4): 374-385.

[240] Semler, M. W., J. P. Wanderer, J. M. Ehrenfeld, J. L. Stollings, W. H. Self, E. D. Siew, L. Wang, D. W. Byrne, A. D. Shaw, G. R. Bernard and T. W. Rice (2017). "Balanced Crystalloids versus Saline in the Intensive Care Unit. The SALT Randomized Trial." Am J Respir Crit Care Med 195(10): 1362-1372.

[241] I am grateful to Dr Ethan Cowan, Emergency Physician at Mt Sinai, New York, US for this observation.

risk threshold, and one set without the threshold is leading to gaming of the system. If the regulatory options available are a threshold of minimal risk (WIC Regulations) or greater than minimal risk (more burdensome EFIC Regulations), this encourages submission of research of substandard design for regulatory review, in order to be permissible under US WIC.

The fourth and final issue in Account 4 relates to general- versus individual-level decision-making. The account shares a tendency in Largent (see Account 2 above) to avoid determining appropriate individual participant treatment by individual level decision-making. Instead general estimations may determine how an individual's benefit is secured and his harm avoided. Securing his benefit is achieved via clinical equipoise, yet other commentators take issue with equipoise as adequate for judging therapeutic risks. For instance, Dickert and Sugarman take issue with both the unsatisfactory requirement[242] and the clinical equipoise requirement (proposed by other scholars as superior to the unsatisfactory requirement) for deciding acceptable risks in emergency research:

> We agree with defenders of the [unsatisfactory] requirement that [emergency research] conducted without consent requires additional protections beyond mere legitimate clinical uncertainty [ie clinical equipoise] in order to prevent exploitation of a very vulnerable population. However, we suggest that what is needed in each case is a careful analysis of whether the risks and benefits of a particular study reasonably can be imposed on participants who have not agreed to be enrolled. p157[243]

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[242] U.S. Government Food and Drug Administration. Exception from informed consent requirements for emergency research, 21 C.F.R. § 50.24. Available from https://www.ecfr.gov/cgi-bin/ECFR?page=browse .See (a)(1), 'available treatments [for human subjects in a life-threatening situation] are unproven or unsatisfactory'. Accessed 26 May 2019

[243] Dickert, N. W. and J. Sugarman (2007). "Getting the ethics right regarding research in the emergency setting: lessons from the PolyHeme study." Kennedy Inst Ethics J 17(2): 153-169.See p156-9 for a discussion of the 'unsatisfactory' criterion.

This careful analysis advocates flexibility outside the confines of an equipoise calculation. It requires analysis of which therapeutic risks are reasonable.

In summary, Account 4 brings to light the difficulty in deciding appropriate risk in emergency research, and tries to swim against a tide of alternative approaches to defining and calculating risk. It should clarify whether its central argument is based on an empirical or normative claim about minimal risk and society, and the type of argument which follows from this. Using minimal risk as a threshold and an algorithm for deciding about risk sets a number of substantive and procedural constraints over decision-making, which are too inflexible overall. They do not allow for countervailing issues which might mitigate risk in certain cases. Nor do they seem to facilitate decision-making since it seems difficult for decision-makers to disaggregate procedures into therapeutic and nontherapeutic types. This causes the minimal risk standard (applicable to nontherapeutic procedures only) to be incoherent when applied in practice in emergency research decision-making. Varying standards of risk and arrangements for managing risk also lead to gaming of the system. Finally, it is doubtful whether basing the research justification wholly upon appropriateness of risks is sufficiently accommodating of all the issues relevant to justifying the research and its decision-making. This is an instance where the account given of the research might limit the proper scope of the decision-making questions which we should address[244].

[244] See also Chapter 1, Section 6 where I discuss in more detail how the account of the research frames the account of decision-making.

3.5.Account 5: Sheehan, Dunn and Sahan

Account 5 is by Mark Sheehan, Michael Dunn and me, Kate Sahan[245]. The main argument in our account is that since research is part of human social flourishing, society should be concerned with research decision-making. Arrangements for regulatory review should reflect this, by arranging a fair process for regulatory review which allows us to investigate society's stake in research appropriately, and allows society to hold research as an institution to account. The account is not specific to emergency research, and in fact focuses on justifying decision-making of social research. Yet it is unique among accounts in this chapter in aiming to justify general research decision-making primarily and completely. It is therefore useful to my justification, since a formal approach to justification, and accompanying reasons, are relevant to the justification for emergency research decision-making.

Our account begins by dealing with a number of objections to governance of social research. Some of the objections are then developed into what we believe is a better articulation of why regulatory review is defensible (or objectionable). We use society to articulate the objections as concerns issuing from society about its relationship with research. Certain sub-accounts of the relationship are tested to see whether they ground a general claim in support of regulatory review. These are: 1) society's concern with the extent of liberty of social researchers; 2) what protections society is owed in research participation (since members of society participate in research); 3)

[245] Sheehan, M., M. Dunn and K. Sahan (2017). "In defence of governance: ethics review and social research." J Med Ethics. 1-7.

accountability of research to society for using its financial or material resources; and 4) society's relation to research as a part of democratic culture which helps society to function. Each sub-account is considered to be a relevant ethical consideration in some cases of research, but none provides a general grounding for regulatory review. In particular, on sub-account 2, protections, we argue that protection of welfare or harm considerations alone cannot offer a general defence for regulatory review. Each research project will be somewhere on a spectrum of benefits and harms. This makes their consideration a relevant consideration, but not the only relevant consideration for decision-making. Also, were this protectionist argument used to defend regulatory review alone, we would be claiming that what matters in the justification for the research and its decision-making is limited to its utility, rather than valuing it for other reasons including for its own sake.

Sub-account 4, society's relation to research as part of a democratic culture, informs the fifth sub-account – enquiry as part of human social flourishing. We use the idea of a democratic culture account to locate enquiry and research 'within the grasp of society, rather than removed from it' p3. We develop this sub-account so that it transcends politics and becomes a fundamental claim about the relationship between enquiry and human social life. Enquiry is a social activity, reflecting collaboratively and on our relationships with others. Such enquiry develops into an iterative process, 'embedded within the functioning of societies, with social life also arising from, and transformed by, enquiry. At the broad societal level, such transformations themselves create and re-create practices of enquiry' p3. Research is understood in these terms as enquiry which has become embedded in institutions such as universities. Research and society thus relate on account of institutionalised enquiry being part of human flourishing, with

which society should be concerned. Flourishing is taken not to pursue utility, but as an engagement in activity which is valuable irrespective of a beneficial or harmful outcome. Society should be concerned with this, because human flourishing involves its members, and it has concerns for its members which are manifested – depending on the political or social theory applied – in certain types or strengths of obligations to them.

Our account then turns from looking at relevant ethical considerations of regulatory review, and the relationship of research and society, to justifying the regulatory review arrangements that follow. Although none of other sub-accounts in the paper (liberty, accountability and protection of welfare accounts) could characterise this relationship satisfactorily, they do provide a relevant set of ethical considerations to use within regulatory review. This is based on the goal of regulatory review being to decide prospectively which research should be conducted. Prospective review is justified not so much because of protection arguments, but because of being able to give the proper consideration to disagreements about whether research should proceed. Review thus necessarily involves reasonable disagreement about which ethically relevant considerations apply, with what priority and weighting, and how disagreements are resolved such that the research is approved or refused.

Table 3: Fair process model for arranging governance

Giving the proper consideration to disagreements is taken to involve a fair process. Therefore we use a model for decision-making which is adapted from Daniels' and Sabin's model of fair process in priority setting in health insurance policies. Daniels and Sabin define a fair process in the Rawlsian sense as 'one that would be agreed on by reasonable persons in the appropriate state of ignorance'. The process is appropriate

given the relationship between research and society which undergirds the governance justification because it maintains a connection between governance and society whom it is serving, so maintaining social accountability.

Daniels and Sabin's model has been adapted to the research context. The square brackets signify our authorial insertions.

1. Publicity: Decisions regarding [research proposals] and their rationales must be made publicly accessible.
2. Relevance: The rationales for decisions should reasonably explain [the grounds for not permitting a piece of research]. Specifically, a rationale is reasonable if it appeals to evidence, reasons and principles that are accepted as relevant by fair-minded people who are disposed to finding mutually justifiable terms of cooperation.
3. Revision and appeal: There must be (1) mechanisms for challenging and resolving disputes about decisions, and (2) more broadly, scope to revise [decisions about the permissibility of research] in light of new evidence.
4. Regulative: The process [of ethical oversight] should be regulated (voluntarily or publicly) to ensure that conditions 1–3 are met.

We note that condition 2) means that the reasons for or against a decision can be properly garnered and weighed in context by a fair minded person who genuinely attempts to consider issues and make judgements impartially, that is 'reasonably'. The process is fair since it can be applied equally to different project instances and is socially accountable. Decision-making in the account is thus procedurally justified, although considerations such as welfare also represent relevant substantive contributions to the content of decision-making.

Criticisms of Account 5

Finally, I turn to criticisms of our account. The strength and weakness of the account's main argument is its generality. It may apply to many different types of research decision-making, but may lack a specificity to aspects of the emergency

research case, such as how to accommodate the inability of participants to consent to the research. Permitting a waiver of consent is not guaranteed on Account 5's argument, since it is something about which we may reasonably disagree, on a case by case basis.

Similarly to Account 1 (Faden), Account 5's main argument depends on a relation between research and society, suggesting through its fair process model society's stake in research may be investigated appropriately. In comparison with Account 1, Account 5 does not accompany its justification with real-world acceptance of reasons. For example, it does not require public disclosures to iterate or reiterate the justification for decision-making. This is despite the conditions listed in the account's model which say decisions should be publicly accessible and revisable on appeal (see Table 3 in this section above, Conditions 1 and 3). Although this might suggest that acceptance of reasons is necessary, altering the argument from justification to justification plus empirical components, the model simply refers to or describes the justification. Were decisions and their reasons examined publicly, the general public should accept them. Public reasons are therefore generally acceptable reasons, not reasons with whose legitimacy the account is concerned. This marks out Account 5 from the other accounts in having a model which does not aim to emphasize empirical components. The potential limitation of Account 5's argument is therefore how it will be meaningful at the real-world level: the model may be taken to be an implementing framework, e.g. resulting in routine public disclosure of ethics committee decisions.

In summary, Account 5 (Sheehan, Dunn and Sahan) is an important example of a formal approach to justifying decision-making. It is valuable for retaining clarity about making my justification with or without empirical components. However, it risks

misunderstandings in real-world contexts over whether the purpose of its model is to describe the justification, or go further and emphasize components for legitimating the justification.

The five accounts above have offered main arguments which may be relevant for justifying decision-making at regulatory review in emergency research. I have examined the strengths and weaknesses of their arguments and reasons with respect to the emergency research decision-making case. I go on to examine a set of reasons for decision-making which the accounts above do not cover in detail.

4. Reasons which are missing from current accounts and are relevant to emergency research decision-making

The US EFIC Regulations contain the requirement for consultation with communities from which participants will be drawn. In Chapter 3, I referred to this requirement as a third party advisory to regulatory review[246]. Nevertheless, the accounts above largely omit discussion of the community consultation (CC) requirement. Those that do refer to it do not use it to provide robust reasons for decision-making at regulatory review, or elsewhere. Such reasons are 'missing' from the accounts. However, the CC makes significant resource demands on researchers and its results should be considered at regulatory review. Also, since its inception it has raised important issues in the literature about the cultural and historical context of emergency research[247]. Because of this, it is important to analyse whether there are reasons for the CC which contribute to the

[246] See Chapter 3, Section 4, Chapter Conclusion.
[247] See Chapter 3, Section 3, Case 5: Polyheme for illustration of such contextual issues.

justification for emergency research decision-making at regulatory review, or elsewhere.

Of the accounts above which do refer to the CC, none gives robust reasons for it. I shall nevertheless analyse the reasons which the accounts do give, before turning to more promising reasons proposed in the CC literature. Account 4 (McRae & Weijer) refers to the CC as an additional protection of subjects. This is also how the US EFIC Regulations themselves and commentators refer to it [248, 249]. Yet the unclear implementation of the CC as an additional protection leaves it open to charges of being responsible for a decline in emergency research activity[250]. Accounts 2 and 3 (Largent and Tigard) say the CC informs the community about the research, such that those who object to the research may understand and use mechanisms for opt-out. In addition Account 2 (Largent) suggests the CC may function to check objections to enrolment from those enrolled during the emergency phase of the research. These accounts give reason for the CC as a way to obtain extra information and clarification about the research. If this is all that the CC accomplishes, then other requirements for public notification and disclosure could cover this, making the CC redundant. Alternatively, since the CC provides information about study opt-out, accounts might be suggesting that the CC substitutes for a form of individual consent. On this claim, the community are seen as potential participants in the research, and the CC allows some of those potential

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[248] Richardson, L. D., R. Rhodes, D. F. Ragin and I. Wilets (2006). "The role of community consultation in the ethical conduct of research without consent." Am J Bioeth 6(3): 33-35; discussion W46-50.
[249] Schmidt, T. A., N. M. Delorio and K. B. McClure (2006). "The Meaning of Community Consultation." The American Journal of Bioethics 6(3): 30-32.
[250] Salzman, J. G., R. J. Frascone, B. K. Godding, T. A. Provo and E. Gertner (2007). "Implementing emergency research requiring exception from informed consent, community consultation, and public disclosure." Annals of emergency medicine 50(4): 448-455.

participants to decline being actual participants were they eligible for enrolment in future. The CC could even be seen to provide community consent on behalf of its members, by combining those information-giving and opt-out functions. Yet both individual and community consent have been rejected as reasons for the CC[251,252]. These reasons are reasonably rejected since a community does not count as a legal proxy and cannot therefore consent for other individuals.

Nevertheless, the literature does not fully shake the idea of the CC as providing community consent to enrol its members (substituted consent) or community approval of the research (part of a local regulatory approval). This is because of how the CC is situated with respect to regulatory review: it is prospective to research approval, advises regulatory review decision-making[253], has a 2-way communication aspect[254], and in some cases results in the research not happening in local collaborating centres[255]. A description by Richardson et al. is salient to these ideas:

> Through… [recruitment using normal consent] … researchers promote the reasonable expectation of respectful treatment, beneficence and goodwill from the research team. This preparatory trust-promoting interaction is not possible in emergency research conducted with an exception from informed consent. By engaging the community prior to the introduction of the study, the research

[251] Biros, M. H. (2013). "Does Community Consultation Matter?" Academic Emergency Medicine 20(1): 104-105. 'Community Consultation is not community consent or veto.'
[252] Richardson, L. D., R. Rhodes, D. F. Ragin and I. Wilets (2006). "The role of community consultation in the ethical conduct of research without consent." Am J Bioeth 6(3): 33-35; discussion W46-50. p34 '…community consultation cannot replace individual informed consent…'
[253] Richardson (2006) *op.cit.*
[254] Shah, A. N. and J. Sugarman (2003). "Protecting research subjects under the waiver of informed consent for emergency research: experiences with efforts to inform the community." Ann Emerg Med 41(1): 72-78.
[255] Biros (2013) op.cit. The article gives the example of a blood substitute study in trauma patients not being conducted in a local community with a large number of Jehovah's Witnesses.

> team has an opportunity to describe their project, hear concerns, and respond as they would when recruiting a subject.p34[256]

CC is not community consent nor is it community study approval. However, it does rehearse discussions of issues which would occur during consent processes, were subjects mentally competent. This situates its value both in a potential future enrolment process, and as part of the current regulatory review process. It suggests two potential reasons for how CC may be contributory to the justification for decision-making at enrolment, and also may be contributory at regulatory review.

A first potential reason for community consultation

From Richardson et al.'s description above, I propose a novel reason for the CC: the CC allows researchers to rehearse what they would say, or 'respond as they would', to eligible emergency patients, in a group of people (the community) who act as test enrolment patients. The CC gives researchers who go on to enrol participants a dry run for ethical considerations which are pertinent to include in their decision-making at enrolment. This novel reason has several advantages over the reasons proposed in the accounts. Firstly, it is more specific than simply being an added protection for participants. Secondly, it does not fall into representation problems of considering the CC as a form of opt-out consent for individuals, or substituted consent on their behalf. Thirdly, it does not see the CC as providing community approval, yet it also takes the CC more seriously than simple advice that may or may not be reflected in the IRB's judgements[257]. The rehearsal may sensitize the researcher to additional information

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[256] Richardson, L. D., R. Rhodes, D. F. Ragin and I. Wilets (2006). "The role of community consultation in the ethical conduct of research without consent." Am J Bioeth 6(3): 33-35; discussion W46-50.

[257] Biros, M. H. (2013). "Does Community Consultation Matter?" Academic Emergency Medicine 20(1): 104-105. On p105 Biros notes that communities believe their concerns will not be taken into account to

relevant to ethical decision-making at enrolment. Similarly, it is likely to sensitize the community to the details of the particular study. However, increased sensitivity does not ground the reason for it. Rather, it demonstrates a future part of the decision-making justification which happens at enrolment.

The value of the process of rehearsal is indicated in the CC conceptual literature. For example, Biros sees the point of such a rehearsal of issues with the community as demonstrating respect for future participants:

> CC provides a concrete means of community engagement, is an easy method of providing education about research concepts, and is a show of respect for the individuals who may someday be our research subjects p105[258]

Biros refers to a 'show of respect' because actual participants worthy of respect cannot be identified at this stage in the research. This indicates that respect for participants matters irrespective of not being able to obtain their consent (a point I will argue for in more detail in Chapter 5). At this preparatory stage before the research, the rehearsal demonstrates (legitimates) part of the decision-making justification which will follow at enrolment. Similarly, Richardson indicates the point of such rehearsals might be to demonstrate trustworthiness:

> Although community consultation cannot replace individual informed consent, it gives the researchers a chance to demonstrate that their study will uphold the community's expectations for trustworthy research practice. p33

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effect study changes. This is also a point I make in Chapter 3, Section 2.5, based on FDA guidance which says the IRB may override community objections to a study.

[258] Biros, M. H. (2013) *op.cit.*

Such demonstrations are exercises to legitimate future decision-making (whether such decision-making includes considerations of respect for persons, or other considerations such as trustworthiness). We might take Richardson to suggest that demonstrating the research is trustworthy functions as a semi-replacement for individual consent, given that some have said trust-building is a function of consent[259]. But since the community may not consent for other individuals, perhaps demonstrating the research is trustworthy to the community functions as partial local approval of the research. In which case the CC forms part of regulatory review decision-making. I shall examine decision-making at the level of participant enrolment and the role of respect in Chapter 5 (in particular Chapter 5, Section 4). Here below, I shall examine whether trustworthiness between the research and the community is a reason for decision-making at regulatory review.

A second potential reason for the CC

A second reason for the CC is that it may communicate good will towards the community in the research enterprise. The research is therefore worthy of trust and approval by the community. This is supported by Kerasidou's conceptual analysis of trust in research, which gives the following characterisation of trustworthiness:

> Trustworthiness relates to the person who is being trusted. It refers to the exhibit of characteristics of the trustee, which indicate that the trustee has good will towards the trustor. A person can be characterised as trustworthy when she "acknowledges the value of the trust that is invested in [her, and] uses that to help [her] rationally decide how to act"p45[260]

[259] Kerasidou, A. (2017). "Trust me, I'm a researcher!: The role of trust in biomedical research." Medicine, Health Care and Philosophy 20(1): 43-50 p44
[260] Kerasidou, A. (2017) *op cit*.

Trustworthiness is taken to be what should be proven in the trust relationship, in order to build or maintain it. A trust relationship exists or is indicated within research relationships where one party in the relationship is vulnerable:

> in order for trust to still be relevant in biomedical research, it needs to be demonstrated that one of the parties assumes a participant stance, namely it assumes a vulnerable position and opens itself up to be validated or betrayed by the other party p47 *ibid*

On this conceptualisation of trustworthiness and the trust relationship, it is possible to characterise a trust relationship between community and research, which the CC builds or maintains through displays of trustworthiness. The claim is that the CC shows the community that the research trustee acknowledges the value of trust which is invested, and uses that to help rational decision-making. Community members would therefore be the object of exhibited characteristics of good will during the CC process. They could also be said to adopt a vulnerable stance with respect to the research. This is because of claims that certain target emergency research communities suffer social and economic disadvantage (SED) which disproportionately affects their health (I shall give examples of this below). The second proposed reason for the CC would then run as follows:

> *Regulatory review should build trust between the emergency research trustee and the community trustor through the CC. This is if we take trust to be a required reason in the justification for decision-making at regulatory review*

To defend this proposed reason I firstly examine the premise that trust is a required reason in the justification for decision-making at regulatory review. This involves working out the identity of the emergency research trustee. Secondly, if regulatory

review is the trustee, or represents the trustee, should we require the CC to build trust in respect of the trust relationship in all cases?

Firstly, the premise that trust is required to justify decision-making at regulatory review. The first clarification to make is about the nature of the trustee. Do we take the emergency research trustee to be the individual emergency researcher or research, emergency research as an institution, or regulatory review of emergency research? All three trustees may be implicated in a relationship with the community. The individual researcher or research should be trusted to uphold ethical treatment of enrolled individuals; the institution of emergency research should also be trusted more widely; and systems which purport to decide ethically about emergency research should also be trusted. In all but the last case, the trust-building which happens is between the community and trustees other than regulatory review. In which case, trust would not belong as a reason to regulatory review's own justification. Rather, it would belong to the ethics of the individual research(er), or institution of research as a whole. In that case, regulatory review would facilitate others' trust-building efforts when it holds the CC. This means for the proposed reason to attach to regulatory review's justification, we need to take regulatory review decision-making itself to be the trustee in the research relationship. Or to be part of the institution of emergency research which should demonstrate its trustworthiness, so representing the institution of emergency research in its trustee role.

The second clarification within this premise is therefore why trust would be required of regulatory review decision-making, and whether it may represent the institution of emergency research. Trust may be required of regulatory review given the phenomenon

of continued scepticism of research, even when it is closely regulated, and trustors may ostensibly rely on those regulations for acceptable treatment[261]. Trust would therefore be a relevant consideration in the ethics of regulatory review decision-making where regulations are implemented. In addition, I contend there is particular cause among certain target emergency research communities to distrust emergency research as an institution, and those bodies making decisions about its acceptability. This is because the emergency research literature reports a trend between communities in emergency research and social and economic disadvantage (SED)[262, 263, 264, 265]. For example, Morrison notes that 'racial minorities and people of low socioeconomic status are disproportionately represented' within emergency patient groups. He reports this is either due to distrust coming from the SED groups involved, or hesitation from recruiters to enrol them, described as an issue of 'access' to clinical trials[266]. This trend associates emergency research with complex wider issues of social inequality in emergency healthcare. In Chapter 3, I noted how such issues arose in a target African-American community in the Polyheme study, and were linked to the ineffectiveness of the CCs which were attempted[267].

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[261] Kerasidou (2017) *op. cit.* p47
[262] Shah, A. N. and J. Sugarman (2003). "Protecting research subjects under the waiver of informed consent for emergency research: experiences with efforts to inform the community." Ann Emerg Med 41(1): 72-78. Especially p77
[263] Nichol, G., E. Huszti, J. Rokosh, A. Dumbrell, J. McGowan and L. Becker (2004). "Impact of informed consent requirements on cardiac arrest research in the United States: exception from consent or from research?" Resuscitation 62(1): 3-23. p7
[264] Morrison, C. A., I. B. Horwitz and M. M. Carrick (2009). "Ethical and Legal Issues in Emergency Research: Barriers to Conducting Prospective Randomized Trials in an Emergency Setting." Journal of Surgical Research 157(1): 115-122..
[265] Feldman, W. B., S. P. Hey and A. S. Kesselheim (2018). "A Systematic Review Of The Food And Drug Administration's 'Exception From Informed Consent' Pathway." Health Affairs 37(10): 1605-1614.
[266] Morrison (2009) *op. cit.* p118
[267] See Chapter 3, Section 3, Case 5: Polyheme

Some of the literature which discusses the SED trend similarly claims the CC should be a requirement of regulatory review in order to address issues of social inequality. For instance, Nichol et al. suggest that while regulatory review may be able to address the recruiter hesitation issue at enrolment, without community involvement it may struggle to address the prior question of social inequality in the communities involved[268]. Richardson et al. also claim that the CC may have wider socioeconomic impacts, resulting in 'a more equitable distribution of risks, benefits, and burdens, and in additional protections and benefits for both participants and non-participants'p34[269]. Shah and Sugarman also note the potential value of the CC in this regard, though they are more equivocal about its chances of success[270]. This is because they claim that SED trends might make effective CC particularly difficult:

> the history of research abuses of ethnic minorities might impede…[CC]… simply because community members might be hesitant to allow investigators into their communities to discuss proposed research. ibid. p77

Also, as they quote from a paper by Dula[271],

> "The infrastructures in many large urban cities are so chaotic, neglected, and poverty-stricken that researchers will encounter problems in finding a safe place to go [for community discussions]." ibid. p77

[268] Nichol et al. (2004) *op. cit.* p7
[269] Richardson (2006) *op. cit.*
[270] Shah & Sugarman (2003) *op. cit.*
[271] Dula, A. (1997). "Bearing the Brunt of the New Regulations: Minority Populations." Hastings Center Report 27(1): 11-12.

This echoes the finding by Holloway that community distrust can prevent effective CC from occurring[272]. Shah and Sugarman yet conclude the CC is valuable in securing trustworthiness and recognising social issues which have led to scepticism:

> Mechanisms to ensure the trustworthiness of proposed research activities should be put in place in an effort to build trust in medical research. Frank community-based discussions with sincere efforts to gauge opinions of community members might serve to address suspicion of medicine and medical research in certain communities. p77[273]

The description of 'mechanisms to ensure trustworthiness' indicates that trust may be required of regulatory review as an integral part of emergency research as an institution. This is given that institutions are capable of developing moral character and an attitude of good will towards research communities[274].

In summary, so far I have argued that a general phenomenon of research scepticism is enhanced in the emergency research case, since at least some target emergency research communities are highly sceptical of the research as an institution. This is due to an SED trend which causes them to assume a vulnerable participant stance. This stance is indicative of being the trustee in a trust relationship. This potentially motivates the need for demonstrations of trustworthiness from regulatory review decision-

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[272] See Chapter 3, Section 3, Case 5: Polyheme where I consider community responses described in Holloway, K. F. C. (2006). "Accidental communities: Race, emergency medicine, and the problem of PolyHeme (R)." American Journal of Bioethics 6(3): 7-17

[273] Shah, A. N. and J. Sugarman (2003). "Protecting research subjects under the waiver of informed consent for emergency research: experiences with efforts to inform the community." Ann Emerg Med 41(1): 72-78.

[274] Kerasidou, A. (2017). "Trust me, I'm a researcher!: The role of trust in biomedical research." Medicine, Health Care and Philosophy 20(1): 43-50. p48

making. Regulatory review, through the CC, may represent itself or a mechanism within institution of emergency research in its trustee role.

However, do phenomena about scepticism and SED in some communities give sufficient cause to make the trust relationship something generally required? This marks the second part of my analysis of the proposed second reason for the CC: whether we should require the CC in all cases. If we take trust to be motivated by the SED status of some communities, this looks to constrain the requirement only to research where social inequality, or complex social issues, are a factor. Additionally, even with these constraints applied, residual questions linger over whether the CC properly represents the marginalised communities involved, and so will stem the scepticism and build the trust required. Secondly, will holding the CC demonstrate trustworthiness, and if it does, will this build trust? Holding CCs may not reliably result in increased trust or decreased scepticism because of views that trustworthiness demonstrations do not automatically build trust[275]. This speaks to a wide literature on trust which notes the problem of trusting well. It matters that we place our trust in trustworthy people and institutions and deny trust to the untrustworthy[276]. Some have also argued that scepticism and suspicion are separate concepts from distrust, and so are not remedied by measures to improve trustworthiness or trust[277]. In which case, this questions the existence of a trust

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[275] Jones, K (2013). Distrusting the Trustworthy. In: Reading Onora O'Neill. D. Archard. (2013). Oxfordshire, England ; New York, Routledge. At p191, Jones quotes a passage from Baier: '" Trust me! " is for most of us an invitation which we cannot accept at will – either we do already trust the one who says it, in which case it serves at best as reassurance, or it is properly responded to with, "Why should and how can I, until I have cause to?" (Baier 1986: 244)'

[276] O'Neill, O (2013). Responses. In: Reading Onora O'Neill. D. Archard. (2013). Oxfordshire, England ; New York, Routledge. p238

[277] O'Neill, O. (2002). Chapter 5: Licence to deceive? In: A question of trust. The BBC Reith Lectures 2002. Cambridge, Cambridge University Press. O'Neill notes that "We may constantly express suspicion, but it is not at all clear to me that we have stopped placing our trust in others"

relationship between emergency research and communities, and holding the CC as reflecting an underlying reason of trust. Scepticism and suspicion are either conceived as separable from the concept of trust, or unwarranted empirical lapses of trusting well, where we should trust but do not[278,279]. Either the trustor (the community) or the trustee (regulatory review) may be responsible for those lapses. In the latter case, through the CC, regulatory review may purport to be community-facing and responsive, but functions to undermine trust in regulatory review or the institution of emergency research. This makes the CC an example of a so-called toxic trust remedy that undermines the trustworthiness of which it is meant to provide reassurance[280].

In summary, it does not seem plausible that an underlying reason of trust justifies the requirement of the CC within regulatory review decision-making. It is evident that enhanced scepticism of emergency research (ER) in certain target ER communities plus the context of ER may be a relevant ethical consideration. However, it is not clear that trust is the deficit we should seek to resolve in holding the CC, nor that by holding the CC we can reliably increase trust. This does not mean that the SED status of certain target communities and wider issues of social inequality and socio-cultural context are irrelevant in deciding about the research. However, trust has not been found to be the reason which makes their consideration a requirement within the justification for decision-making.

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[278] O'Neill, O. (2002). Autonomy and trust in bioethics. Cambridge ; New York, Cambridge University Press. p141

[279] Jones, K (2013). Distrusting the Trustworthy. In: Reading Onora O'Neill. D. Archard. (2013). Oxfordshire, England ; New York, Routledge. p187. Jones notes that one of trust's pathologies is the problem of "unwarranted suspicion".

[280] Jones, K (2013) *op.cit.* p192

Perhaps instead of looking to trust as a reason, which as a concept seems beset by sociological and empirical complexities, we should take the CC simply to be a way to acknowledge and assess social injustice in certain cases of the research. This would cohere with the broader role for justice in Account 1's (Faden's) argument. Its obligation 5 requires users of the Learning Healthcare System to monitor whether their proposed activities yield disproportionate benefit in already advantaged groups, or disproportionate burden in already disadvantaged groups, and take steps to reduce inequalities. This releases the CC from any outcome-oriented approach such as trust-building, which is hard to do reliably, and avoids the sense that research approval is contingent on building trust. But it does ask researchers to consider the community actively as part of acknowledging and assessing the impact of the research on social injustice. This consideration is at the level of communities themselves so making it a requirement in certain cases to hold the CC. If the CC is only required in certain cases, a residual issue is who decides when a CC should be held. This recommends an alteration of the CC decision-making process into two stages: the first stage would be a discursive account from researchers about whether social injustice factors in their target communities of interest with respect to the impact of the planned research. This account is judged by the IRB which thereby is implicated in considering social injustice in each instance of the research. The second stage would be holding a CC if social injustice is thought to be a factor meriting active consideration of the community. During the CC, researchers seek out clarification from communities on SED and socio-cultural factors particularly, as well as giving information and taking community questions as described by existing guidelines.

To sum up this section, I showed that the first proposed reason for the CC – rehearsal – is a legitimation of justificatory reasons: it allows researchers to rehearse what they would say to eligible emergency patients, in a group of people (the community) who act as test patients for enrolment. This may incidentally yield extra knowledge about the community (researcher sensitization to community) or the research (community sensitization to the research) in certain cases. However, its underlying value is respecting the individual participant as a person which will occur at enrolment. The second proposed reason of trust-building has not been possible to defend. Despite relevant considerations of social inequality and socio-cultural context, it is not possible to justify the CC as part of regulatory review on the basis that regulatory review should build trust between emergency research and the community. However, in certain cases where social injustice is a factor, holding a CC acknowledges and assesses the impact of the research on social injustice.

Neither reason for the CC in its current form is justificatory: the first reason legitimates future decision-making; the second justifies decision-making only in certain cases. However, my account here has given a clearer sense of the important considerations which the CC reflects when it happens. Since neither reason is justificatory, we should not always hold a CC. It should be held in cases where social injustice is a factor, and so in holding a consultation researchers can assess impacts on social injustice, rehearsing future decision-making in a way which takes social factors into account. This makes rehearsal of decision-making contingent on social injustice being a relevant factor.

In its alternative two-stage form which I have suggested above, the CC indicates a justificatory reason within its first stage: regulatory review decision-making should include consideration of social injustice as a requirement, and should decide whether the second stage of the CC (active consultation) is appropriate, since it will be appropriate in certain cases. Holding the active consultation is then the outcome of decision-making at regulatory review which has judged social injustice factors to merit further acknowledgement and assessment at the community level.

5. Offering a justification of decision-making at regulatory review

In general, I have shown the arguments in all five accounts are applicable to the justification question of research decision-making at regulatory review with a waiver of consent. Accounts have taken similar approaches to justifying this. Firstly, they have sought theoretical agreements (Accounts 1 and 5: Faden and Sheehan), or attempted to predict individual choices through grouped choice and interests (Accounts 1,2, and 4: Faden, Largent and McRae & Weijer). Secondly, they are similarly concerned to ensure welfare based on: grouped prediction, intent, or process algorithm (Accounts 1-4: Faden, Largent, Tigard, McRae & Weijer). Thirdly, most accounts use some procedural reasons to justify their arguments (procedural fairness in Accounts 1 and 5: Faden and Sheehan; procedural consistency in Account 4 McRae & Weijer).

A further similarity between accounts is in their inclusion of frameworks or models to accompany their arguments. One interesting finding from my analysis is how frameworks or models could have a dynamic effect on accounts by emphasizing components which might be used to legitimate justifications. This happened when accounts used frameworks to describe how the argument was meaningful in the real world, but in doing so made a further claim (implicitly or explicitly) about the argument's

reliance on real-world contexts or facts relating to the decision-making involved. This reliance could undercut the justification itself (for example, see Section 3.2. Account 2: Largent above). This tendency for frameworks to have dynamic effects on arguments has implications for the type and coherence of my own justification and future accounts based on justification type arguments (see Section 6.2 Implications for future accounts below).

These similar approaches (and similar dynamic effects when using frameworks) indicate unifying factors in the quest to justify the research or its decision-making. However, no single account has been sufficient for the complete justification for decision-making. In particular, accounts have largely omitted discussion of the community consultation (CC) requirement. Therefore, below I propose a novel justification for decision-making at regulatory review. This brings together reasons from different accounts, together with additional reasons I have argued for with respect to the CC, to form the justification. Within the justification, I connect reasons developed in this chapter to the five developed themes from Chapter 3 (See Chapter 3, Section 2 Themes 1-5). These themes established an ultimate focus on the US EFIC Regulations as presenting the more demanding challenge for justifying decision-making.

5.1. Reason 1: regulatory review secures commitment to the common purpose of ER under a waiver of consent, using a combination of general and (delegated) individual level decision-making

Based on Account 1 (Faden), regulatory review general-level decision-making is permitted to presume a waiver of consent applies in emergency research (ER) on a theoretical commitment to do the research without express consent, since ER advances learning. It presumes we have common interests in learning and so would commit to the research, without requiring our actual commitment or agreement to this.

This reason offers an acceptable challenge to the foundational status of consent in ER. This reflects one half of a strategy within ER regulations to reconcile the seemingly contradictory elements of rule exception (consent waiver) with rule norm (normal consent), by a presumption that the waiver applies (see Chapter 3, Section 2.1 Theme 1). Yet ER includes research with more uncertainty about therapeutic benefits and risks than research or 'learning activities' of Account 1. Because of this, Reason 1 is less than a social obligation (as Account 1 has it) to agree to the permissibility of the research, or be a participant, under the waiver. Being less than an obligation motivates regulatory review to delegate and monitor decision-making at enrolment to ensure permissibility of research under the waiver in individual cases. This reflects the other half of the reconciliation strategy, which ensures the presumed waiver applies at the individual level (see Chapter 3, Section 2.2 Theme 2). As part of ensuring a waiver applies, decision-making ascertains the likelihood of individual objection, or checks research is not against an individual's interests. This amounts to at least lack of objection to the commitment to the common purpose of the research, if not a type of theoretical commitment (since we cannot obtain actual permission from the participant himself). This individual-level decision-making is delegated because regulatory review is not in a position to judge individuals' objections or consider them appropriately in other ways. For this reason, I contend that Reason 1 for regulatory review entails a delegated decision-making role for the physician-researcher at individual participant enrolment. I shall argue for this role in Chapter 5.

Both Accounts 1 and 5 ground their arguments for theoretical agreement to the research in a relationship between research and society, and in social accountability, which Account 1 instantiates practically. Decision-making practices described in the ER

regulations also underline social accountability. Firstly, public disclosures are supportive empirical components of the commitment to permit the research without consent. They maintain a level of transparency in decision-making (see Chapter 3, Section 2.4 Theme 4: external and internal disclosures). Secondly, documenting of various processes, such as attempts at consent, sharing information within the research establishment, and using the results of community consultation, gives regulatory review the means for society to hold it to account (see Chapter 3, Themes 2: ensuring waiver is permissible, 4: external and internal Disclosures, and 5: Community Consultation).

Importantly, Reason 1 is contingent on empirical components. Presuming the waiver is permissible, by reason of a theoretical commitment, entails a check to ensure the presumed waiver applies. This means the reason does not belong to a pure justification argument since checks are made at the individual level. Instead ensuring the presumed waiver applies at the individual level embodies the commitment in a real-world context. A further two reasons further characterise the terms of the first reason.

5.2. Reason 2: regulatory review judges risks appropriately because they are reasonable in process and substance.

Risks in emergency research decision-making are justified by procedural criteria, appropriately constrained by some substantive criteria. Procedural criteria largely follow the comparative assessments of risks used in the wording of the US EFIC Regulations:

> (a)(3)(iii) Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.[281]

[281] U.S. Government Food and Drug Administration. Exception from informed consent requirements for emergency research, 21 C.F.R. § 50.24. Available from https://www.ecfr.gov/cgi-bin/ECFR?page=browse Accessed 26 May 2019

Reason 2 maintains the concept of 'reasonable' as opposed to 'minimal risk'. It decides about risk, as with other relevant ethical considerations, in a reasonable way, speaking to the fair process justification of Account 5 (Sheehan). In particular, the process in Account 5 is justified because rationales for decisions should appeal to 'evidence, reasons and principles that are accepted as relevant' (see Section 3.5, Table 3, Relevance condition). Similarly, the risk wording above points assessment to relevant factors, assessed reasonably. This properly accommodates the range of emergency research therapeutic designs which we should decide about (from head to head comparisons of standards of care, up to novel drug or device studies (e.g. CTIMPs or INDs)). This is because although minimal risk, like the term 'unsatisfactory available treatments', may be designed to express due caution about permissible risk under the waiver, it is not meaningful in practice. It leads to substandard research designs being put forward, and avoidance of the regulations for higher risk studies, which use overly-demanding, proxy processes to manage risk. The requirement for internal disclosures between agencies may be a symptom that these processes are bureaucratic and should be refined (Theme 4: external and internal disclosures). This is because, while sharing regulatory information is a noble intention in all types of research, requiring it as a proxy for risk determination in the emergency research case has two negative effects. Firstly, it increases the idea that the research is especially controversial. Secondly, it suggests fundamental disagreement between agencies about whether the research risks are acceptably determined.

Substantive criteria which appropriately constrain procedural aspects comprise general assessments that the research will be responsive to medical need of the

condition suffered by the research cohort, and that existing science about the research and proposed therapeutics supports the research going ahead (Chapter 3, Theme 1: presuming waiving consent is permissible, and Theme 3: acceptability of risks and benefits). But, on my argument, these criteria do not specifically require that current available treatments should be 'unproven or unsatisfactory' in order to permit the use of experimental therapeutics (see US EFIC (a)(1)). This is because it is too difficult to determine the level of dissatisfaction with current treatments such that the 'unsatisfactory' requirement is fulfilled. The 'unproven or unsatisfactory' requirement is therefore incoherent for justified decision-making.

Reason 2 connects to the delegated aspect of Reason 1 (a delegated decision-making role for the physician-researcher at individual enrolment). Presumptive procedural and substantive criteria assessed at regulatory review are complemented by individual-level checks. This makes the reason sympathetic to the physician-researcher's intent to benefit idea in Account 3 (Tigard). However, this intent should be accompanied by more concrete procedural and substantive support. This is because benefit in therapeutic research is uncertain (and particularly uncertain in novel drug studies). So relying solely on physician-researcher intent gives the researcher too much unilateral authority over deciding that individual benefit will occur, and therefore risks are appropriately mitigated. Accordingly I propose to use the reasonable person standard (RPS) in Account 2 (Largent) to offer this support. In doing this, I take checks of the reasonable person to support the justificatory basis for the RPS (see Section 3.2, Criticisms of Account 2). Instead of entirely presuming that the reasonable person would agree based on converged choices and interests, we also check for existence of objections at the individual level.

5.3. Reason 3: through the community consultation, regulatory review allows consideration of social injustice

The Community Consultation (CC) does not offer a justificatory reason for regulatory review decision-making in its current form. Currently, it legitimates parts of the justification for decision-making at enrolment (the idea of the rehearsal or dry run of issues to consider at enrolment). This connects to the delegated aspect of Reason 1 (a delegated decision-making role for the physician-researcher). In its current form, it may also in certain cases acknowledge and assess the impact of the research on social injustice, so justifying regulatory review's attention to this.

Since neither reason is justificatory, the CC should not be a requirement in its current form. However, by altering the CC to be a two-stage process, we may require regulatory review to consider the relevance of social injustice within its decision-making. Social injustice will be a relevant consideration in research in certain target emergency research communities with enhanced scepticism about the research due to background trends of social and economic disadvantage (SED). Where social injustice is found to be a factor, holding active consultation in the community is further acknowledgement and assessment of the impact of the research on social factors. This pinpoints use of the active part of the reformed CC process to cases such as Case 5 Polyheme (see Chapter 3, Section 3), where being sensitive to socio-cultural context is clearly vital for ethical decision-making.

6. Chapter conclusion: bringing reasons to bear on the emergency research regulations

In conclusion, in Chapter 4 I have shown that the justification for decision-making at regulatory review comprises three main reasons:

1. The reason of common purpose. Regulatory review secures commitment to a common purpose of emergency research under a waiver of consent, via a mixture of general and individual (delegated) decision-making. This reconciles the seemingly contradictory elements of rule exception (consent waiver) with rule norm (normal consent). Reason 1 depends on a delegated decision-making role for the physician-researcher at individual enrolment. This reason should be legitimated through public disclosures which underline accountability of the research to society. Reason one is characterised further by Reasons 2 and 3:

2. The reason of reasonable risks. Regulatory review may decide risks using a mixture of both procedural and substantive criteria. By conducting comparative assessments of risks which are reasonable in relation to certain factors, the decision-making is procedurally justified. Substantive criteria which appropriately constrain these procedural aspects are checks on background science, and of the direct response of interventions to the patient's medical needs. They are complemented by a specific check of the reasonableness of the research for the individual patient: there is no reason to think the actual patient would object. This anchors the level of risk by orienting it to individual well-being and to an extent interests, and is a way to add concrete support to the idea of intent to benefit participants. As with Reason 1, this specific check happens within the physician-researcher decision-making role delegation.

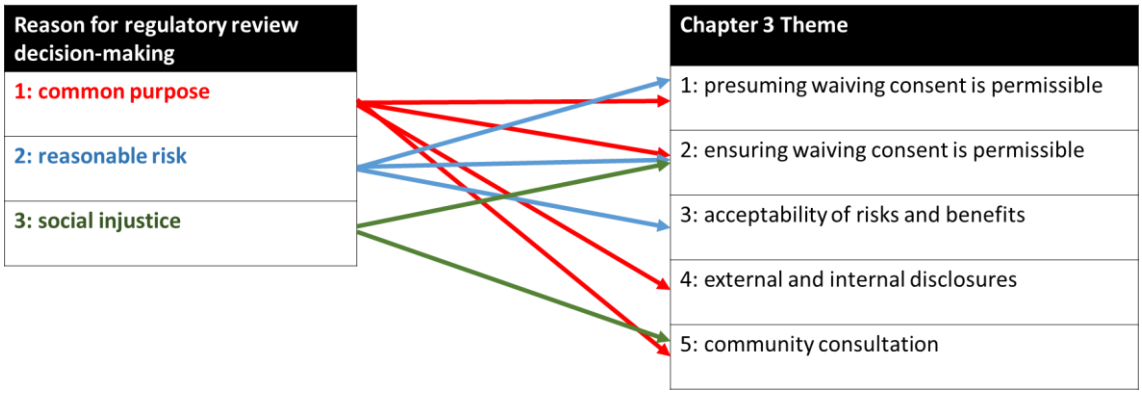
3. The reason of acknowledgement and assessment of social injustice. Community Consultation is split into a two-stage process. Firstly, researchers and regulatory review undertake a discussion about whether social injustice in their communities of interest will be impacted by the research. Secondly, if social injustice is found to be a relevant

factor, an active consultation is held, which is oriented towards elucidating those factors, in addition to other issues raised by the community. During the consultation, researchers may actively rehearse future decision-making at enrolment, also with an eye to social factors.

Within this justification there are supportive empirical components. These components rely on practices and attitudes with respect to the decision-making involved. In Reason 1, these components iterate the terms of theoretical agreement and provide proofs of social accountability. In Reason 2, they support the justificatory basis for the reasonable person standard. In Reason 3, they acknowledge and assess social injustice factors and other issues in a community forum.

Reasons are consistent with the main themes of emergency research regulations, and decision-making practices therein, which I identified in Chapters 2 and 3. I illustrate this by the following figure (see Figure 2 below). However, as a result of the work in this chapter, there are some implications for future accounts justifying decision-making using frameworks, and for future regulations and policy.

6.1. Figure 2 illustrating fit of reasons to Chapter 3 developed themes



6.2. Implications for future accounts

The tendency which I have identified in the accounts for frameworks to have a dynamic effect on arguments may have implications for how future scholars should

make and interpret such accounts. It may be helpful to distinguish where accounts are offering what we could term an implementation framework (e.g. Accounts 1, 2 and 4: Faden, Largent and McRae & Weijer) and where they are offering a modelling framework (e.g. Account 5: Sheehan et al.). Implementation frameworks may have a dynamic effect: they may signify or emphasize empirical components of accounts and the connection of accounts to the real world level. This emphasis should be checked for coherence and defended. Modelling frameworks are more descriptive of how the argument would operate in the real world: they have no dynamic effect, and the account's arguments stand without empirical emphasis.

6.3. Policy implications

The justification I have established has several implications for the emergency research regulations and related policy and guidance documents. With respect to Reason 1, it is currently unclear that the regulations are pursuing a *justified* strategy to reconcile rule exception (consent waiver) with rule norm (normal consent), that this strategy relies both on presuming and ensuring the waiver is permissible, and that general- and individual-level decision-making both matter. Importantly, the strategy is not contradictory but validates both obtaining and waiving consent where appropriate. Making the strategy clearer to RECs and IRBs which conduct regulatory review may help them to review the research, and permit waivers, with more confidence. This is provided they can rely on the delegated aspect of Reason 1 to complete the strategy.

With respect to the delegated aspect of Reason 1, my justification therefore argues for more emphasis on the importance of attempts at consent and proxy consent (US EFIC (a)(5-6, 7(v)), both in how they are worded and what implementation follows. I detail these policy changes in the next chapter (Chapter 5), which argues for the role of

the physician-researcher in realizing the value of individual decision-making at enrolment. In Chapter 5, I will also recommend changes to terms and clauses I identified in Chapter 3 which may lead to side-lining of individual decision-making (see Chapter 3, Section 2.1 discussion of: deferred consent; practicability and feasibility; and presumptions of mental incapacity).

With respect to Reason 2, the justification argues for the removal of the 'unproven or unsatisfactory' available treatment criterion at US EFIC (a)(1). This also has implications for related wording from other regulations which requires too low or too indeterminate a threshold for appropriate risk. Examples of this are 'unduly' and 'negligible' risk wordings from the UK Mental Capacity Act. On the matter of minimal risk itself, the US EFIC Regulations do not contain this term and I argue should not be altered. Their sister regulations, the US WIC Regulations, do contain a minimal risk threshold, but are not fit for purpose in the emergency research case, and are causing inferior research designs to be put forward. Changes to these and other regulations with minimal risk thresholds (e.g. EU Regulations) should be made by the addition of a clause for emergency research which replaces minimal risk with a more nuanced criterion based in the concept of reasonable risk. Further work is required to understand exactly how reasonable risk should be conceptualised in emergency research, and where to set a reasonable threshold for permissible risks without consent.

With respect to Reason 3, I argue for a rewording and reconceptualization of the CC. It is not simply an external third party advisory to regulatory review, as I suggested in the conclusion of Chapter 3. Nor is it an under-determined additional protection of participants. It is rather a way to reflect on social injustice factors both as part of

processes internal to regulatory review, and in the community where relevant. This requires a change to the US EFIC Regulations. The CC should be altered from being a requirement in its current form. However, a process should be added to regulatory review which requires consideration of social factors and social injustice, with potential for an active CC in the community. When the CC is held in the community, policy should clarify that assessment and impact of the research on social injustice should be at the fore. Policy should also emphasize that an active CC gives scope for researchers to 'rehearse' future ethical decision-making at enrolment.

Finally, I call for further conceptual work which compares the emergency research regulations with rules and procedures of other regulatory agencies. This is to ascertain what is behind the internal disclosures requirement (Chapter 3, Theme 4: external and internal disclosures). If the internal disclosures requirement is simply a reflection of dysfunction between different regulatory agencies, this is a reason to refine the system, not continue with disclosures alone. Similarly, the fact of additional requirements in the US EFIC Regulations, such as the internal disclosures requirement, should not stand as proxies for participant protection from risk by simply discouraging applications for regulatory review.

Chapter 5: The role of the physician-researcher in the decision-making justification: ensuring the waiver is permissible

1. Introduction

In Chapters 2 and 3, I argued that general and individual decision-making areas correspond to presuming versus ensuring the waiver of consent is permissible. Together the areas work to reconcile the exception to the rule of consent (the consent waiver) with maintaining the rule (normal consent) where possible. In this chapter, I suggest physician-researchers play a significant decision-making role in ensuring the waiver is permissible per patient, so reconciling consent waiver and consent use appropriately. As part of this, I examine how the role is to avoid provoking an issue of deep concern in research ethics: the use of individual patients by researchers as merely a means to scientific ends. I shall refer to this as the 'deep concern of exploitation'.

In the first part of this chapter, I build on my sense from the Chapter 3 that general decision-making exerts an unintended influence over individual-level decision-making, side-lining it in practice. This starts to provoke the deep concern of exploitation as it suggests patients are not worthy of individual moral consideration. Justifications in the literature recognise the exploitation concern and even advocate greater physician-researcher accountability to offset it. But they stop short of seeing this as within the power of the regulations, and properly-justified decision-making, to resolve.

In the second part of this chapter, I show how individual-level decision-making at enrolment, securing 'participant-satisfied conditions', potentially resolves the exploitation concern. However, its effectiveness is limited by an 'enrol only' option at enrolment. Building on the previous chapter, I propose the physician-researcher is

uniquely positioned to realize the full justificatory value of individual-level decision-making, and discuss the moral strengths and weaknesses of her in so doing. One weakness is the potential for the physician-researcher's conflicts of interest to reintroduce the exploitation concern. As part of addressing this concern, I propose the regulations should clarify the physician-researcher's freedom to enrol *or exclude* eligible participants. This could be done by adding a brief additional decision-making step to the enrolment process, consistent with current emergency research regulations. Finally, I consider possible objections to the addition of this decision-making step.

2. How individual-level decision-making comes to be side-lined in practice

The exception from, or waiver of, consent regulations governing emergency research enrolment were instituted because the context of emergency research makes the possibility of securing consent or proxy consent unclear and unlikely. In some regulatory jurisdictions this led to a ban on emergency research because consent could not be obtained, and therefore the research fundamentally conflicted with the foundational status of normal consent in research ethics[282].

Researchers operating under the current emergency waiver regulations benefit from permission to waive normal consent legitimately. Regulations are based on general-level decision-making which presumes waiver permissibility, coupled with individual-level decision-making to ensure a waiver is permissible per participant. In Chapter 3 I argued that together these pursue a reconciliation strategy of rule exception (consent waiver)

[282] Biros, M. H., J. W. Runge, R. J. Lewis and C. Doherty (1998). "Emergency medicine and the development of the Food and Drug Administration's final rule on informed consent and waiver of informed consent in emergency research circumstances." Acad Emerg Med 5(4): 359-368. p362 especially.

with rule norm (normal consent). However, I also noted an unintended influence of general- over individual-level decision-making in certain terms and clauses within the regulations: firstly, in the use of deferred consent; secondly, in the language of practicability and feasibility; and thirdly through baseline presumptions of insufficient mental capacity to consent (see Chapter 3, Section 2.1). This risks side-lining individual-level checks to ensure the waiver is permissible.

Here I give an example of how side-lining is happening in practice, using a published emergency research study which was approved under the current emergency research regulations. This is the 2014 HEAT PPCI trial of bivalirudin versus heparin in acute myocardial infarction (heart attack)[283]. The research uses general-level decision-making (presumptive permission in principle to waive consent) to avoid the need for individual-level decision-making. Its researchers praise the waiver permission because they believe it allows them to pursue an enrolment 'policy' of 'Every Patient, Every Time'. This policy was used because it helped to all but eliminate selective inclusion practices:

> The study design also sought to address another common limitation of the randomised controlled trial; recruitment of only a modest proportion of the potential, eligible population. Such selective inclusion can restrict the generalisation of study findings in clinical practice… Very sick, elderly, or frail patients, those with low socioeconomic status, women, and individuals from ethnic minorities are often not approached for study participation… [with the waiver, we] set ourselves the demanding goal to randomise all eligible patients p1850

[283] Shahzad, A., I. Kemp, C. Mars, K. Wilson, C. Roome, R. Cooper, M. Andron, C. Appleby, M. Fisher, A. Khand, B. Kunadian, J. D. Mills, J. L. Morris, W. L. Morrison, S. Munir, N. D. Palmer, R. A. Perry, D. R. Ramsdale, P. Velavan, R. H. Stables and H.-P. t. investigators (2014). "Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial." Lancet 384(9957): 1849-1858.

The permission in principle for the waiver is interpreted as allowing a policy which obviates the need for individual assessment to ensure the waiver is permissible. This allows HEAT PPCI to recruit 97% of eligible candidates. Yet such permission in principle is not designed to address selective inclusion problems, even though these might be important in their own right. Using the permission in this way therefore capitalizes on the absence of checks and balances that would normally occur as part of consent or consent waiver processes. The 'selective inclusion' above is regarded as bias: unhelpful under-inclusion of certain subgroups in research with effects on quality of the sample or fairness of inclusion. On the other hand 'selective inclusion' may be appropriately selective: enrolling individuals from certain subgroups may not be in their clinical interests (e.g. sick, elderly, frail, women whose pregnancy status is unknown), or may perpetuate disproportionate burdens of participation (e.g. in socially and economically disadvantaged groups) [284, 285]. The policy above denies the chance for physician-researchers to be selective in an appropriate and defensible way, since it discourages individual-level decision-making.

The example above indicates that individual assessments may be side-lined because ensuring the waiver is permissible is not seen as important, or is seen as covered by the initial presumptive permission secured at regulatory review. This implies the judgements of physician-researchers about enrolling individual patients do not matter, or actively harm research quality. It also implies participants lacking capacity are not

[284] Holloway, K. F. C. (2006). "Accidental communities: Race, emergency medicine, and the problem of PolyHeme (R)." American Journal of Bioethics 6(3): 7-17.
[285] Morrison, C. A., I. B. Horwitz and M. M. Carrick (2009). "Ethical and Legal Issues in Emergency Research: Barriers to Conducting Prospective Randomized Trials in an Emergency Setting." Journal of Surgical Research 157(1): 115-122.

worthy of moral consideration as individuals. This starts to provoke a deep concern of exploitation: use of patients instrumentally as a merely a means to secure scientific ends.

3. Analysing the deep concern of exploitation using a justification for non-voluntary enrolment in emergency research

Of the accounts which justify emergency research from Chapter 3, Account 3 by Daniel Tigard engages most fully with avoiding provoking the deep concern of exploitation[286]. The account characterises the particular exploitation of patients in emergency research as being related to the seriousness of their condition: if their condition is seen as hopeless, experimentation without consent exploits; however, if it is nearly hopeless and tractable with the proposed therapeutics, experimentation is permissible. In this way Tigard motivates therapeutic success as a primary aim of the research while recognising it will often transpire as secondary or incidental to the research's aims:

> In the case of a clinical trial for emergency situations where informed consent is impossible to obtain, physicians are morally permitted to pursue the advancement of medical knowledge, but only as a byproduct of pursuing therapeutic success.p350

The account also emphasizes a particular mind-set for physician-researchers towards the 'present patient' at enrolment. They should prioritise therapeutic intent:

> Non-voluntary subjects must first be patients, and physicians as researchers must remain physicians first and foremost. In Jonas's words, the "gain to knowledge and future therapy is incidental to the *bona fide* service to the present patient."p350

[286] Tigard, D. (2016). "Emergency Preservation and Resuscitation Trial: A Philosophical Justification for Non-Voluntary Enrollment." Bioethics 30(5): 344-352.

The account supports the idea that to avoid concerns of exploitation, the physician-researcher's attitude towards the patient in front of her at enrolment is important. By suggesting also that physician-researchers should be held 'initially and continuously' accountable, this supports the idea that they should give reason for the waiver in principle (when they make their case for the research at regulatory review) and continuously in practice (at instances of enrolment). Finally, by noting that the double-effect justification may be waived if emergency patients are competent to consent, the account ostensibly associates the justification with individual level assessments and decisions.

However, ultimately the account stops short of seeing the value of individual level decision-making to its arguments despite the emphasis on the physician-researcher as above. This is because of a simplistic view of the waiver regulations, described by Tigard as 'simply waiving the requirement of obtaining and documenting informed consent' p346, 'a negation of accepted standards' p348 and a 'minimalistic justification of being exempted from the usual, accepted standards for research' p351[287]. There is no justificatory value in the waiver regulations or regulatory review decision-making for Tigard. This is even though the structure of his central argument – keeping research and individual considerations in a properly-prioritized balance – is sympathetic to the general and individual decision-making areas I proposed in Chapter 3. Stopping short of valuing decision-making – in particular at the individual level – is also because of an inability to see emergency patients as persons, despite their lack of mental capacity and

[287] Tigard, D. (2016). "Emergency Preservation and Resuscitation Trial: A Philosophical Justification for Non-Voluntary Enrollment." Bioethics 30(5): 344-352.

thus autonomy. The implication is that because of the absence of capacity and autonomy (at least in the case of exsanguination cardiac arrest sufferers), neither participants nor proxies are worthy of individual assessment.

4. A framing for consideration of participants in emergency research ethics

What is needed is a better way to reflect the moral worth of individuals as participants in the research, despite their lack of mental capacity. To do this I shall frame the issues of consent and governance in emergency research ethics in a way which gives space for individual participant consideration under the waiver of consent.

The focus of research ethics is to balance consideration of the aims of research with consideration of individual research participants. This is reflected in the regulatory model of research ethics comprising a bipartite structure of approval at regulatory review plus individual consent (see Chapter 1, Section 5 for the full definition of this model). In emergency research as in other clinical research, the main aim is to advance the common good by gaining scientific knowledge[288]. In therapeutic designs, gaining knowledge is partially offset by the aim to offer direct therapeutic benefit to participants. Nevertheless, while some participants will benefit by being in the research itself, mostly the benefit will fall to future patients not in the research whose care is advanced by the knowledge gained. Because of this, individual research participants deserve separate consideration in deciding whether the research should proceed. Two

[288] Brody, H. and F. G. Miller (2003). "The clinician-investigator: unavoidable but manageable tension." Kennedy Inst Ethics J 13(4): 329-346.

foremost principles in biomedical ethics which describe this consideration are respect for autonomy and respect for persons.

Beauchamp and Childress are thought to have introduced the principle of respect for autonomy, even though their *Principles of Bioethics*, first published in 1979, refers to it as 'Respect for persons', alongside other principles of beneficence, non-maleficence and justice[289,290]. Faden and Beauchamp go on to use autonomy in their definition of informed consent as autonomous authorisation[291]:

> An informed consent is a specific kind of autonomous choice (or action), an autonomous authorization by patients or subjects. p277

An informed consent is given 'if a patient or subject with (1) substantial understanding and (2) in substantial absence of control by others (3) intentionally (4) authorizes a professional (to do I).' p278.

This emphasizes the importance of respecting autonomy whose expression is specific to the participant, or relates to the individual. It also ties respect-for-autonomy's value to the ability to obtain informed consent. In contrast, respect for persons is not dependent on obtaining consent and consequently is thought by some to be the more important overarching principle. The Belmont Report describes it as follows:

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[289] Beauchamp, T. L. and J. F. Childress (2013). Principles of biomedical ethics. New York, N.Y. ; Oxford, Oxford University Press.
[290] Lysaught, M. T. (2004). "Respect: or, how respect for persons became respect for autonomy." J Med Philos 29(6): 665-680.
[291] Faden, R. R., T. L. Beauchamp and N. M. P. King (1986). A history and theory of informed consent. New York, Oxford University Press.

> Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection[292]

The principle allows us to respect non-autonomous individuals, such as emergency patients, as well as those with autonomy. Some have argued that Beauchamp and Childress are contradictory in the way they approach respect for persons. Lysaught, for example, argues that they call it an 'aspect of the principle of autonomy' meaning that '[a]utonomous and non-autonomous persons are decoupled and respect applies only to the former'[293]. For the purposes of this chapter, I take respect for persons as described by Belmont: as not dependent on autonomy, and importantly not dependent on obtaining consent, provided appropriate protections are in place (such as risk thresholds). I use this principle to access moral consideration for participants who are incapable of giving consent to take part in emergency research. Such a principle might encompass respect for a participant's own welfare, including assessment of clinical benefits pertinent to his own clinical presentation. It might also involve recognition of his status as a human being, e.g. aspects of his own wishes or choices, even if the emergency setting does not allow deep discernment of this.

In the next sections, I explore the above proposition. I show that parts of the waiver regulations attend to consideration of individual participants directly, and aim to fulfil functions of respect for persons (rather than autonomy), and protection of individual participant welfare. Other parts attend to considerations more generally of the

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[292] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). The Belmont report: Ethical principles and guidelines for the protection of human subjects of research, Washington, D.C.: U.S. Government Printing Office.
[293] Lysaught, M. T. (2004). "Respect: or, how respect for persons became respect for autonomy." J Med Philos 29(6): 665-680.

research, aiming at general welfare protection and appropriate governance such that the research is conducted ethically.

5. Structure in the regulations

Here I use the US EFIC Regulations to describe how the regulations attend to consideration of individual participants directly. In Chapter 1, I gave a rationale for focusing on US EFIC as the more demanding justification challenge to address within the thesis[294]. In this chapter, the therapeutic orientation of the requirements of US EFIC is also particularly suitable for examining how the dual clinical-research role of the physician-researcher may be harnessed in support of her justified decision-making (which I argue for below in Sections 6-7).

The regulations to waive consent in emergency research can be specifically structured into two types of conditions: a) those satisfied on assessment of the general profile of the research, without reference to individual participants; and b) those to be satisfied on assessment of each individual participant up until he is enrolled to the emergency phase of the research. Through this the regulations secure two types of waiver permission: presumed permission, or permission in principle, to conduct the research with a waiver of consent; and ensured permission to enrol individual participants with a waiver (or consent). The types of conditions are distinguished by i) what type of waiver permission is secured (presumed permission or ensured permission), ii) who secures it (regulatory review or physician-researcher), and iii) environment (non-emergency situation prior to, or after the research; emergency phase

[294] See Chapter 1, Section 3, on the role of emergency research regulations in the thesis.

of the research). The regulations thus have the capacity to consider the individual participant as well as general profile of the research or participant cohort.

5.1. Regulation conditions which are satisfied without reference to the participant in non-emergency situations

Satisfaction of some conditions in Figure 1 depends on decisions made during regulatory review by the institutional review board (IRB) alone, or in consultation with various other decision-makers. I will refer to these as review-satisfied conditions. Their satisfaction does not depend on a participant-specific assessment and happens outside the emergency enrolment encounter. They are listed in the box below:

Review-satisfied conditions: waiver conditions whose satisfaction does not depend on participant-specific assessment during the emergency
I take the following conditions to be satisfied by decision-making of the expert clinical community. This community could be represented by the current evidence base and literature about the emergency condition in question. It could also be represented by actual clinicians (the research team or an external consultant) who contribute to the IRB's decision-making: (a)(1) unproven or unsatisfactory treatments recommend experimentation on this class of patient-participants (a)(2)(ii) the intervention must be given before proxy consent is 'feasible'; (a)(4) waiver makes the study practicable. (a)(2)(iii) there is no way to identify individuals in advance of the research (a)(3)(i-ii) individual participants could directly benefit because of general views of need for intervention, and supporting preclinical or earlier phase studies (a)(3)(iii) risks are reasonable for participants who could directly benefit, given what we know about how the class of patient-participants will fare in the research versus current standards of care. (a)(7)(iv) an independent data monitoring committee conducts oversight of the study **In contrast, the following conditions stipulate the IRB, lay community or Sponsor as decision-makers:** (a)(5) the IRB conducts continuing review of the study (a)(7)(i)-(iii) community consultations and public disclosures give opportunity for opinion about aspects of the study before it starts and after it has completed (b) the IRB is responsible for checking that consent-to-continue procedures are in place

(c) and (e) the IRB should keep records of study records, and records of unsuccessful waiver applications (d) The study Sponsor or research teams should submit certain other regulatory applications alongside waiver applications (e) Sponsors should disclose unsuccessful applications for the waiver to regulators and others

Conditions assess acceptable risks in order to protect the well-being of participants in general, and also to take measures to protect the reputation and liability of institutions involved (see paragraphs c, d and e for measures of accountability like record keeping). The process of satisfying these conditions secures permission in principle to conduct the research under a waiver.

5.2. Regulation conditions which are satisfied by individual participant assessment during the enrolment encounter

Satisfaction of other conditions depends on decisions which happen from the time the patient presents as eligible for the research up until the point of his enrolment by the physician-researcher (I will call this period of interaction the enrolment encounter). This encounter does not actively involve the IRB which conducts regulatory review or other stakeholders since they are not present. I will refer to these conditions as 'participant-satisfied conditions'. They involve the patient or proxy himself and the physician-researcher. These conditions are listed in the box below:

Participant-satisfied conditions: waiver conditions whose satisfaction depends on participant-specific assessment during the emergency up to the point of enrolment
(a)(2) (i) [each] participant's medical condition must be assessed to confirm that they cannot give normal consent; (a)(5) An investigator commits, 'if feasible', to attempting to contact each participant's proxy for normal consent within a specific therapeutic window of opportunity and documents this attempt; (a)(6) Informed consent documents and procedures (which have been pre-approved by the IRB) are to be used with participants or proxies where 'feasible'.

(a)(7)(v) In the absence of a legal proxy, an investigator commits 'if feasible' to attempting to contact a non-legal proxy, a family member, to see if he objects to the research [an informed refusal type of enrolment option in the research]. She documents this attempt using IRB-approved procedures and information

Satisfying these conditions results in ensuring permission to enrol each individual participant under the waiver, or reverting to consent. This potentially achieves two things pertinent to showing respect for persons: 1) a recognition in principle of the moral worth of participants as individuals; 2) a practical effort to look at a participant's individual features, even if information about him is limited. Satisfying these conditions becomes a practical iterative way to respect potential participants as persons, and of giving moral consideration to them and any available proxies or family members.

However, the potential value in meeting participant-satisfied conditions is currently limited in two ways. Firstly by an 'enrol only' option at enrolment itself, and secondly by under-described responsibility for the physician-researcher in satisfying the conditions. Again this makes ensuring the waiver is permissible seem unimportant. I describe the 'enrol only' option at enrolment in emergency research in Figure 1 below. The only current exclusion route open to participants is where they fall outside the waiver regulations. This occurs when they have mental capacity and can exclude themselves from the research. I examine the second limitation of under-described responsibility of the physician-researcher in Section 6 below.

5.3. Figure 1: Enrol only option when participant-satisfied conditions are met

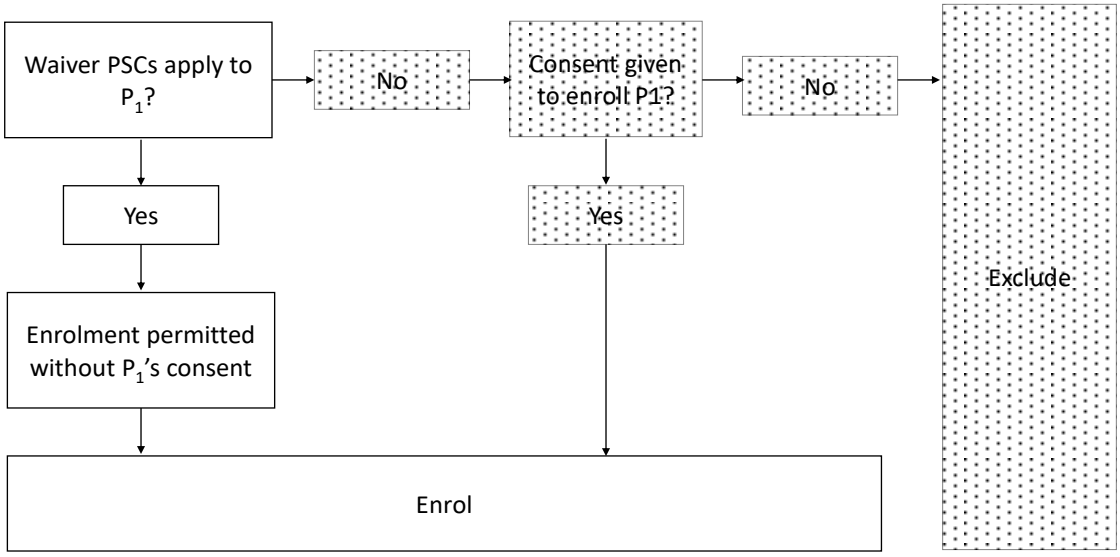


Figure 1: in this flowchart, review-satisfied conditions have already been met. Flowchart shapes with a clear background track the decision-making for enrolling a given patient, P_1, who meets participant-satisfied conditions (PSCs). The only option, once PSCs apply, is to enrol him. Conversely, flowchart shapes with a shaded background track decision-making outside the waiver regulations where P_1 (or proxy) is found to have mental capacity, and enrolment reverts to normal (or proxy) consent processes. Under normal consent processes, P_1 (or proxy) chooses whether to be enrolled or excluded, reflecting consent or no consent.

6. Realizing the value of participant-satisfied conditions

The physician-researcher, or research associate working with lead clinicians in emergency departments, is uniquely positioned to make decisions about interventions or care pathways the patient undergoes during the enrolment encounter. In preparation for the research commencing, she or colleagues may have undertaken active community consultation, and have had a chance to rehearse discussions of issues which would occur during consent processes were participants mentally competent. This may have sensitized her to issues which are relevant to consider in her decision-making about

individual participants such as particular social injustice factors[295]. During the enrolment encounter itself, she assesses patients and proxies for mental capacity; she commits to making attempts to obtain consent or proxy consent; she keeps consent documents ready for use and records attempts to contact proxies. Finally she enrols the participant. This initiates a relationship between patient-participant and physician-researcher, as the physician-researcher visually observes the patient, looks at his medical history, and interprets subtle informational cues from him and any proxies. These cues do not necessarily depend on him being conscious, or his proxy having sufficient capacity. I contend that in doing this the physician-researcher carries out a responsible role for individual-level decision-making. This is currently under-described and under-valued as potentially contributing to the justification for decision-making. She is in a position to secure a modest level of respect for individual patients as persons, a relation of the respect for individual autonomy principle which does not depend on patients having capacity at enrolment.

Therefore I propose that through designating and articulating a justified role for the physician-researcher as responsible for fulfilling participant-satisfied conditions, we may realize their full value and so the value of individual-level decision-making to the overall justification question. This involves recognition that the role has moral aspects. Some aspects strengthen the case to take the role of the physician-researcher seriously in realizing the full value of participant-satisfied conditions, thereby respecting participants as persons, and contributing to the decision-making justification for the

[295] See Chapter 4, Section 4, A first potential reason for the community consultation, and Chapter 4, Section 6 Chapter conclusions. Here I describe how community consultation allows for a rehearsal of issues relevant to decision-making at enrolment.

research. Others raise potential barriers to taking the role seriously, but are not (as I argue below) insurmountable.

6.1. Moral aspects of the role

It is important to emphasize that physician-researchers will necessarily have moral intuitions about enrolment, since emergency research is clinical research and so enrolment or exclusion will impact patient care. When therefore she is judging whether to enrol a participant, she considers whether or not she ought to enrol Patient x because of y reasons. Y reasons will be many and complex, but some will be based on respect for the participant as an individual ('x') person, and others on whether his individual interests (including clinical welfare) are promoted or held back by enrolment.

To claim the opposite – that physician-researchers would not be able to respect patients as persons or look to their individual interests – is highly contentious. It would claim they lack basic humanity, as well as professionalism, and experience and training in clinical and research ethics. Even if we were to characterise physician-researchers as not fully responsible for appropriate patient consideration, e.g. that they are just part of an approved study or following an approved process, it would be unconvincing to claim from this that the role does not have moral aspects. At least some moral judgement and choice will continue to attach to it. Given this, it seems likely the physician-researcher's role is at least one of the variables for justifying decision-making at the individual level and overall.

Overlooking important moral aspects of the role might not only miss the opportunity to accord participants appropriate consideration, but also harm physician-researcher integrity. However, by acknowledging the role's moral aspects, we must address its

potential moral weaknesses, namely the physician-researcher having potentially harmful conflicts of interest (COIs).

6.2. A moral concern about this framing of the role: the issue of conflicts of interest

On this objection, the value of this role is questionable because physician-researcher decision-making is inappropriately constrained by conflicts of interest. If true this would again provoke the deep concern of exploitation: physician-researchers would use individual patients merely as a means to scientific ends, since they have vested interests in pursuing those ends. In order to examine the objection fully, I first analyse how conflicts of interest (COIs) are conceptualised in research. Then I give the objection and its rebuttal.

There is a substantial literature on financial and non-financial COIs in research[296,297,298,299,300]. Churchill examines COIs by first analysing the logic of the physician-researcher's dual care-research role. He starts by saying 'When a physician is an investigator as well as therapist to his patient, or —to put it the other way around— when a patient is not only a patient but also an experimental subject to his physician, the relationship between them can become exceedingly complex'[301]. He then uses five indices of the relationship to explore its logic. The concluding section of the paper describes the tension or conflict between the competing claims of therapy and

[296] Capron, A. M. (1974). "Informed consent in catastrophic disease research and treatment." Univ PA Law Rev 123(2): 340-438.
[297] Churchill, L. R. (1980). "Physician-investigator/patient-subject: exploring the logic and the tension." J Med Philos 5(3): 215-224.
[298] Thompson, D. F. (1993). "Understanding financial conflicts of interest." N Engl J Med 329(8): 573-576.
[299] Levinsky, N. G. (2002). "Nonfinancial conflicts of interest in research." N Engl J Med 347(10): 759-761.
[300] Brody, H. (2011). "Clarifying conflict of interest." Am J Bioeth 11(1): 23-28.
[301] Churchill L (1980) *op. cit.*

investigation, which he thinks are 'irreducible and necessitate a choice on the part of physician-investigators as to where their priorities lie' p222.

Levinsky stresses that while financial conflicts of interest (COIs) have received much attention, non-financial COIs in research are a more insidious and complex type to identify and manage. While noting that the interests of participants and researchers may in some cases align, he acknowledges that 'an investigator's interest in career advancement, although entirely ethical and appropriate in itself, may conflict, or appear to conflict, with the interest of subjects in minimizing the risk of psychological harm, physical injury, or death. Such potential nonfinancial conflicts are 'inherent in all research involving human subjects' p760. Thompson also makes a distinction between conflict and the appearance of conflict in his discussion of financial COIs:

> [the aim of COI management] …is to prevent these secondary factors [e.g. scientific prestige] from dominating or appearing to dominate the relevant primary interest [e.g. patient protection] in the making of professional decisions.[302]

Brody advances the following criteria for defining a COI:

> 1. The physician has a duty to advocate for the interests of the patient (or public). 2. The physician is also subject to other interests—her or his own, or those of a third party. 3. The physician becomes a party to certain social arrangements. 4. Those arrangements, as viewed by a reasonable onlooker, would tempt a person of normal human psychology to neglect the patient's/public's interests in favor of the physician's (or third party's).[303]

[302] Thompson, D. F. (1993). "Understanding financial conflicts of interest." N Engl J Med 329(8): 573-576.
[303] Brody, H. (2011). "Clarifying conflict of interest." Am J Bioeth 11(1): 23-28.

Based on these accounts, COIs are an expression of a complex care-research role or patient-physician to participant-researcher relationship. They are inherent, and so cannot be eliminated but should be recognised and managed in some way. They form through the physician being party to, and developing partiality towards, certain social arrangements such as the status of a research career or scientific progress in research. If this partiality neglects patient interests, also known as 'primary interests' in the literature, then the COI occurs. A COI may be wrong because the conflicted interests in the mind-set of the person increase the possibility of unintentional, knowing, or intentional harms. Or a COI may be harmful because it has a downstream harm which can be attributed to the COI. Yet the existence of a COI does not necessarily determine unethical intent or harmful outcome.

COIs may present with a psychological subtlety. Physician-researchers may wilfully or unconsciously respond to COIs in making decisions. They may cut corners in the enrolment procedure, or exert pressure on proxies to consent, all the while believing they are still putting the patient's interests first, while unconsciously favouring the research. If the mind-set of the physician-researcher as a moral agent is in question, this is problematic in the case of the role described. The physician-researcher might take what turns out to be an appropriate enrolment decision, but based on morally inappropriate reasoning.

Where harms are attributed to COIs in research, they are envisaged as risks of harms, or actual harms, borne by participants. For example, Levinsky notes that COIs '…cannot be prevented or eliminated, but … must be recognized if the risk to research subjects is to be minimized' p760. Individual harms as serious as participant death have been

reported, with COI causality established through major financial interests and a flagrant disregard for the welfare of individual subjects[304]. Also recent accounts in the public health literature claim epidemiological studies are able to track trends between COIs and harms at the population level[305,306]. However, empirical evidence as to the extent and cost of COIs is generally considered lacking[307].

In the emergency research case, taking financial COIs to be controlled for, it will be hard to attribute a COI to harm outcomes. Harms through COIs are hard to distinguish from the common 'harm' of emergency research outcomes of mortality and serious morbidity. It also happens that those outcomes of mortality and morbidity are standard measures, at least in epidemiologic science, to measure COI harm[308]. This leads to a 'noise' problem of every enrolment instance susceptible to the charge of a COI.

COIs may undermine legitimacy of individuals carrying out roles in research, or research institutions more generally. The perception of a COI can be just as damaging as an actual COI, irrespective of whether it has a harmful outcome. This speaks to Levinksy and Thompson's comments above about it being as necessary to prevent the 'appearance of conflict' or 'appearance of dominating secondary interests' as actual conflict.

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[304] Jacmon, H. (2018). "Disclosure is Inadequate as a Solution to Managing Conflicts of Interest in Human Research." Journal of Bioethical Inquiry 15(1): 71-80.
[305] Goldberg, D. (2016). "On Physician-Industry Relationships and Unreasonable Standards of Proof for Harm: A Population-Level Bioethics Approach." Kennedy Inst Ethics J 26(2): 173-194.
[306] Goldberg, D. S. (2018). "The Shadows of Sunlight: Why Disclosure Should Not Be a Priority in Addressing Conflicts of Interest." Public Health Ethics: phy016-phy016.
[307] Rosenbaum, L. (2015). "Understanding bias--the case for careful study." N Engl J Med 372(20): 1959-1963.
[308] Goldberg, D. S. (2018). "The Shadows of Sunlight: Why Disclosure Should Not Be a Priority in Addressing Conflicts of Interest." Public Health Ethics: phy016-phy016.

7. The COI-based objection to the physician-researcher's role

From the above analysis of the concept of COIs, I base the potential moral weakness of the physician-researcher's role on the following objection:

> *The physician-researcher should not discharge her role (administering participant-satisfied conditions) and enrol participants, as by doing this she will favour, unconsciously or otherwise, secondary interests (e.g. her scientific interests in the research) over primary interests (of treating the potential participants appropriately, including considering their interests). Favouring secondary interests in this way is to the detriment of participants and counts as a COI, whether or not this risks downstream harms.*

7.1. Rebutting the objection

7.1.1. Conscious or unconscious favouring of the research

On this part of the objection, COIs are complex, inherent features of the care-research dual role. It is then hard for the physician-researcher to recognise when COIs are at work, irrespective of whether they are likely to harm. The literature also suggests it will be difficult for the physician-researcher to motivate herself to reflect objectively on situations when COIs may arise and she may be at risk of neglecting the participant's interests. For example, Jacmon further cites the related issue of 'situational challenges', described as 'pressure to recruit participants, the appeal of prestige, subordination issues, or simply positioning oneself for future work' p76[309]. Such challenges reflect the especial circumstances of the emergency research enrolment context and its current

[309] Jacmon, H. (2018). "Disclosure is Inadequate as a Solution to Managing Conflicts of Interest in Human Research." Journal of Bioethical Inquiry 15(1): 71-80.

'enrol all' emphasis. This might contribute to an initial lack of motivation to reflect, and do so objectively.

To encourage reflection, the COI literature proposes forms of recognition and disclosure. For example Levinsky argues that recognition can be initiated by institutionally-based training for researchers[310]. In the proposed role, the role itself would help to better motivate reflection and thus recognition of COIs than current emergency enrolment practices, where physician-researchers are discouraged from considering participants' interests[311]. So too, extra training and perhaps in-role prompts might help to stimulate reflection about COIs, for example, whether the motivation for an enrolment decision is due to unconscious secondary interests.

Disclosure is often seen as a sanitising or 'sunlighting' process, especially in industry conflicts [312, 313]. As applied to the physician-researcher and patient-participant relationship, the physician-researcher discloses COIs to the patient-participant, and this makes both parties wiser about the dynamics influencing the proposed enrolment opportunity being offered. Disclosures thus entail there being a consent process within which COIs can be revealed and in some way their wrongness mitigated by the judgement of the participant himself. For example, King and Churchill note that 'the best opportunities for clarifying the differences [between the dual roles of physician and researcher] lie in the consent form and process.' This is because informed consent

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[310] Levinsky, N. G. (2002). "Nonfinancial conflicts of interest in research." N Engl J Med 347(10): 759-761.
[311] See illustration of this discouragement in the HEAT PPCI example above in Section 2.
[312] Jacmon, H. (2018). "Disclosure is Inadequate as a Solution to Managing Conflicts of Interest in Human Research." Journal of Bioethical Inquiry 15(1): 71-80.
[313] Goldberg, D. S. (2018). "The Shadows of Sunlight: Why Disclosure Should Not Be a Priority in Addressing Conflicts of Interest." Public Health Ethics: phy016-phy016.

‘‘‘encourages self-scrutiny by the physician– investigator’’[314]…meaning that the duty to explain the research to potential subjects also provides physician–researchers with an opportunity to make their own views clear to themselves, through articulating them to others’[315]. Miller and Weijer make a related point about duty in arguing for a fiduciary obligation, derived from clinical practice, between participant and researcher in clinical research:

> Management [of conflicting] responsibilities include, most prominently, disclosure of the conflict to the beneficiary [e.g. the potential participant]. With permission of the court or consent of the beneficiary, the fiduciary is usually allowed to continue to exercise her powers… p435-6[316]

On these accounts, lack of ability to disclose is a key part of the problem for the proposed physician-researcher role in emergency research enrolment. Since the patient cannot consent, he cannot mitigate COIs. However, disclosure, while it is transparent about the COI, may act to prevent its mitigation. Goldberg, in his discussion of COIs in population health contexts, makes this point, arguing that ‘[a]t best, disclosure does not work. At worse, it intensifies behavior of partiality’, since disclosures strengthen rather than weaken the influence of the ‘forthcoming’ discloser (the physician-researcher) to the disclosee (the potential participant)[317]. In the emergency enrolment context, influence may be exacerbated if time pressures force the physician-researcher to

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[314] King, N. M. P. and L. R. Churchill (2008). Clinical research and the physician–patient relationship: the dual roles of physician and researcher. The Cambridge Textbook of Bioethics. A. M. Viens and P. A. Singer. Cambridge, Cambridge University Press: 214-221. The authors quote a passage from Capron. Capron, A. M. (1974). Informed consent in catastrophic disease research and treatment. U Penn Law Rev 123: 340–61.

[315] King and Churchill (2008) *op cit.*

[316] Miller, P. B. and C. Weijer (2006). "Fiduciary obligations in clinical research." J Law Med Ethics 34: 424–40.

[317] Goldberg, D. S. (2018). "The Shadows of Sunlight: Why Disclosure Should Not Be a Priority in Addressing Conflicts of Interest." Public Health Ethics: phy016-phy016.

attempt partial disclosures to conscious patients or their proxies, so strengthening their influence without even giving full information. This claim is supported by those who argue that even participants with sufficient mental capacity for consent do not have the expertise to interpret conflict disclosures meaningfully and so are perhaps unfairly made responsible for their management[318]. Having examined the limitations of disclosure in consent, it seems even were it fully possible in the emergency context, it offers nothing especially remedial.

7.1.2. Enrolment is favouring the research over primary interests

This part of the objection seems easily rebutted since the purpose of the role is to elevate the importance of consideration of the participants' interests in a way which is not currently encouraged. Considering primary interests is further promoted by certain documentation conditions of the waiver regulations which hold physician-researchers to account for decisions they make in the role. It is also not the case that every instance of enrolment will favour the research. In some instances, enrolment may hinder the research, for example if a patient is delirious and is hard to 'manage' through the research protocol. In that example, the enrolment decision would be a clear indication that primary interests were favoured over secondary ones.

7.1.3. Favouring of the research is necessarily wrong

On this part of the objection, it is necessarily wrong to favour the research as it will necessarily set back the participant's interests. Favouring the research by enrolment might rather be in his interests as well as the research's interests. This captures the idea

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[318] Jacmon, H. (2018). "Disclosure is Inadequate as a Solution to Managing Conflicts of Interest in Human Research." Journal of Bioethical Inquiry 15(1): 71-80.

of an alignment of interests as noted by Levinsky above. This part of the rebuttal is also supported by the problems of attribution between COIs and harms. It is also the case that over-caution to promote primary interests may under-sample emergency populations who might personally derive benefit from the research[319]. So it seems neither enrolment, nor favouring the research by enrolment, determines existence of COIs, at least ones which set back interests or relate to downstream harms.

Here I summarise the rebuttal. Having COIs in the role is incongruous with its aims to consider participant interests and respect them as persons. This lessens the concern that the physician-researcher will override those interests in favour of scientific interests, particularly if she is held to account for the role. Nevertheless, in-role prompts and training may help recognise where she may unconsciously favour the research. Disclosing potential COIs to participants at enrolment has not been shown to prevent their occurrence and so offers no especial remedial value. Enrolment in the research does not necessarily favour the research over primary interests, particularly given the intention in therapeutic research is to benefit patients. Even where the research is favoured, this is not necessarily wrong although systematic favouring might suggest the mind-set of the physician-researcher is morally suspect. In this respect, the 'enrol only' emphasis of the process of meeting participant-satisfied conditions remains a key part of the objection to the role. It forms a situational challenge, affecting the motivation of the physician-researcher to discharge her role appropriately, and reflect on possible

[319] This recalls the view of the HEAT-PPCI trial above (Section 2) that selective inclusion may under-sample population subgroups, but uses the role to be appropriately selective, rather than over-sample.

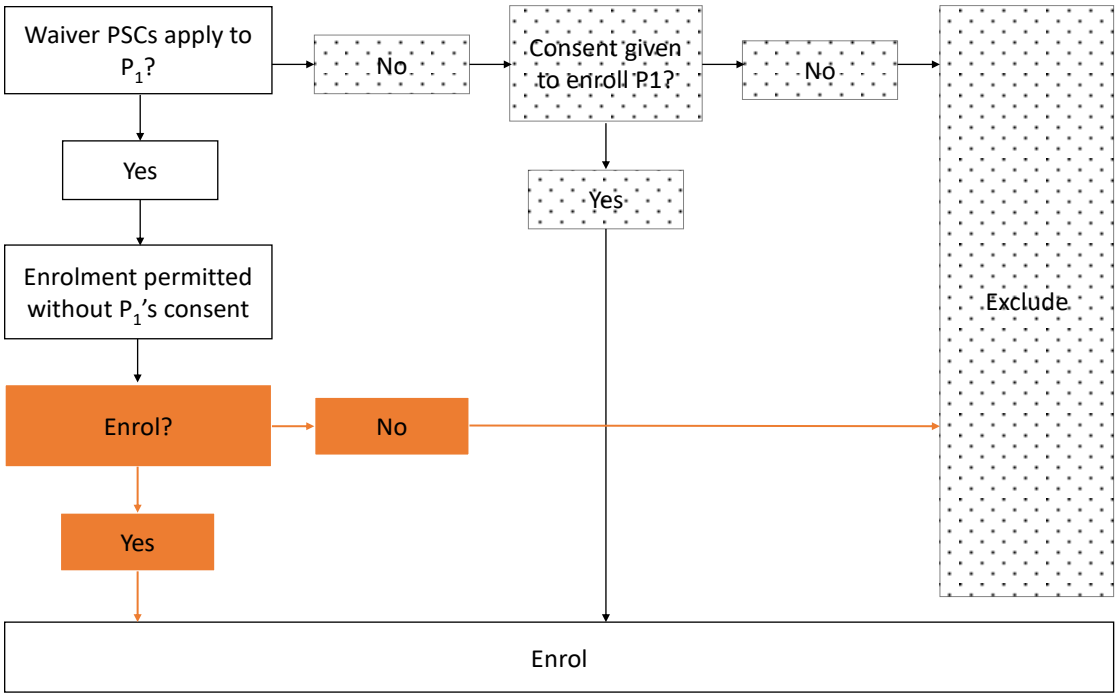
COIs. It also contributes to the perception that COIs are occurring which may undermine the authority of the role, even if based on justified arguments.

8. An additional decision-making step to change the 'enrol only' option

The discussion of the COI-based objection above gives reason to change the 'enrol only' option which concludes the current decision-making process of meeting participant-satisfied conditions. In order to change the 'enrol only' option, and realize the full value of participant-satisfied conditions, I propose adding an implicit decision-making step to the waiver. It allows participant-satisfied conditions to be better realized in practice through removal of the perception that physician-researchers systematically favour the research over participant interests.

8.1. Figure 2: decisional diagram

The revised decision-making process is shown in full in the decisional diagram below. Orange shows the additional decision-making step. This additional step emphases the importance of discharging the role per participant at enrolment, since it requires the physician-researcher to think about whether to enrol, even when P_1 meets eligibility criteria for the research and for a waiver at the individual level. It gives the opportunity to exclude as well as enrol the participant in a way which more appropriately respects him as a person, and considers his individual interests, even within the constraints of the emergency context.



8.2.Objections to the additional step and responses

A number of objections can be raised to the value of this additional step. The objections raised below have merit, but they do not refute the general points that i) the physician-researcher is uniquely positioned to bring her dual care-research role skills to bear usefully on judgements about appropriate enrolment; and ii) the 'enrol only' option is problematic for justifying her role, and for arguing that ensuring the waiver is permissible contributes to the decision-making justification overall. This is granting that discharging her role in this setting will still be complex and will still involve dealing with COIs.

Objection 1: Not enough information about the patient to give reasons for or against enrolling him.

On this objection, there is not enough information of substance about the patient to direct a meaningful decision about whether to enrol or exclude him. In response, I cite

the preparatory sensitization to, and rehearsal of, issues arising from cases where community consultation is indicated (see Chapter 4, Section 4 for full consideration of the reasons for community consultation). I also cite the relationship formed during the enrolment encounter and its subtle informational cues. The emergency research literature on enrolment of conscious emergency cohorts also supports meaningful decision-making based on less demanding forms of communication and informational exchange than consent, such as informed refusal, and brief verbal consent or assent[320,321]. However, it is true that these cues are likely to be rare, especially in majority unconscious cohorts, so entailing decision-making mostly based on basic ideas of participant welfare. On a continuation of this objection, since participant welfare is protected by the review-satisfied conditions which assess appropriateness of risks, the physician-researcher is adding no extra insight to the decision-making. In fact she may be undermining prior risk-benefit analyses which have given reason to include him if she excludes the patient to protect his welfare. In response, I suggest the physician-researcher may yet offer extra assurance that prior general analyses of risk and other factors operate to the benefit of the individual patient concerned.

On an alternative form of the objection, one might suggest that the physician-researcher would need to be a legal proxy to access information sufficient for a decision. This is because proxies have authority and also relevant information about the

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[320] Dickert, N. W., J. Brown, C. B. Cairns, A. Eaves-Leanos, S. F. Goldkind, S. Y. H. Kim, G. Nichol, K. J. O'Conor, J. D. Scott, R. Sinert, D. Wendler, D. W. Wright and R. Silbergleit (2016). "Confronting Ethical and Regulatory Challenges of Emergency Care Research With Conscious Patients." Annals of Emergency Medicine 67(4): 538-545.

[321] Sahan, K. M., K. M. Channon, R. P. Choudhury, R. K. Kharbanda, R. Lee and M. Sheehan (2016). "Refining the Enrolment Process in Emergency Medicine Research." Eur J Cardiovasc Med 4(1): 506-510.

participant they can use in decision-making. But physician-researchers could not legitimately be a proxy for two main reasons. They would firstly encounter problems of designation and secondly of authenticity: they are neither authorised by the patient to take on a proxy role, nor do they have much scope for representing him authentically if there is little to no prior relationship to draw on[322]. Designation raises particular authority issues in the emergency research case since the physician-researcher is the actor who technically decides there is no 'fit' proxy to act for the participant (see (a)(5) in the US regulations). If, through this initial judgement, she also has scope to decide that she will be the proxy, or will be a better proxy than existing candidates for the role (legal proxies or other family members), this seems like too much unilateral influence over the scope of her decision-making role. Condition (a)(5) would also thus need increased external oversight, in order to monitor the increased scope of the role. Such oversight would not fit the urgency of the enrolment context. Authenticity is a problem since there may be no prior relationship between physician and patient, and the disease presentation is urgent. Together, these problems suggest being a legal proxy will not suit the role, and is not guaranteed to access information sufficient for a decision.

Objection 2: Step is just a tokenistic demonstration of consideration, but does not actually consider.

On this objection, it is a mistake to alter the enrolment process as proposed, if all we are achieving is tokenism. Tokenism refers to the physician-researcher demonstrating proper individual-level consideration by that extra decision-making step, but not

[322] Shepherd, V., K. Hood, M. Sheehan, R. Griffith, A. Jordan and F. Wood (2018). "Ethical understandings of proxy decision making for research involving adults lacking capacity: A systematic review (framework synthesis) of empirical research." AJOB Empir Bioeth 9(4): 267-286.

actually considering the individual patient any more meaningfully than before. A rebuttal to this is that tokenism matters as far as managing perceived COIs in her role. To the extent that the perceived COI is a 'victimless crime', i.e. has little actual implication for the participant, the step may an innocuous addition. However, there may still be a concern in the objection that when physician-researchers know the step is partly a perception management exercise, they will not take their role seriously, using the step to enhance their practice. Yet being held accountable for their decision-making will perhaps mitigate this. The step contributes empirical components to the justification. It demonstrates management of COIs and so emphasizes their role has moral weight and responsibility (legitimation of justificatory reasons). It therefore reduces the risk physician-researchers will distance themselves from the responsibility, e.g. saying it resides with the IRB at regulatory review. This risks a kind of responsibility 'hot potato' problem if the IRB also claims it resides elsewhere. As a result, the step reduces the risk of under-designating responsibility such that everyone and no one is responsible for patient enrolment.

Objection 3: Physician-researcher is still insufficiently motivated to manage her conflicts appropriately. Enrolling is still too attractive on balance

On this objection, the step proposed is not a sufficient solution to the problems of managing the dual care-research role, and associated conflicts. I grant that the additional step offers only a modest improvement on how the role is conducted, and how to navigate the complex factors influencing the emergency enrolment encounter. Yet in making a case for the role, I am positive about the professional ethics of physician-researchers, and the strengths of the moral aspects of their role. I also cite the

importance of regulatory review in assisting (rather than undermining) ethical decision-making in the role, as well as holding it to account.

9. Chapter conclusion and policy implications

In conclusion, Chapter 5 shows that current interpretations and justification of the emergency research regulations side-line decision-making at the individual level which ensures the waiver applies to specific participants. Yet regulations specifically attend to consideration of individual participants (through what I have called 'participant-satisfied conditions', or PSCs). This offers a practical iterative way to respect potential participants as persons. The role of the physician-researcher is uniquely positioned to attend to individuals and realize the full value of PSCs, yet is limited by the 'enrol only' option of the current enrolment process. This prevents rebuttal of an objection (the COI-based objection) that her role would systematically favour interests of the research over patient interests. To address this, I have added a decision-making step to the process of enrolment which gives the opportunity to exclude as well as enrol. The step emphasizes the importance of the physician-researcher role, underlining her responsibilities; it also reduces the appearance of COIs and thus the deep concern of exploitation. The role will never completely be free of COIs, and as such is compatible with the parts of decision-making at regulatory review which hold it to account. Overall, however, the role is significant in ensuring the waiver is permissible per patient, so reconciling consent waiver and consent use appropriately.

The arguments in this chapter call for some changes to regulations and associated policy or guidance documents. Firstly, the role of the physician-researcher should be elaborated in the regulations, and its significance emphasised in content and placement of appropriate clauses. For example, clause (a) of the US EFIC Regulations referring to

responsibilities of the IRB could be contrasted with a new clause (b) referring to responsibilities specific to the physician-researcher. Within clause (b) existing requirements relating to the physician-researcher role could be grouped (see Section 5.2 above for these requirements or 'participant-satisfied conditions'). Guidance about the role should detail how information about the patient is gathered and used at enrolment. This is by a combination of rehearsal of issues relevant to enrolment at prior community consultation (where this is indicated), and subtle informational cues about the patient gleaned during the enrolment encounter itself. This guidance should also stress that the role is not a proxy consent for the patient, but aims to respect him as a person given his incapacity to consent.

Secondly, it is appropriate to revise guidance documents to include the extra decision-making step I have proposed. Given the urgent context, it is too demanding and risky with regard to patient care to make this additional step part of a regulatory requirement. However, on the arguments above, guidance should emphasize that it is permissible for the physician-researcher, as part of her role, to exclude as well as include participants who nevertheless meet criteria for the waiver. Detailing this step underlines the moral weight and responsibility of the physician-researcher's role, and avoids the 'hot potato' problem of the researcher and IRB both shunning responsibility for enrolling the patient without consent.

Thirdly, I call for the removal of language which implies deferred consent is permissible. This is most evident from wording in the EU Regulations which states informed consent may be obtained 'after the decision to include the subject' (EU

Regulations 35 1.)[323]. 'Deferred' is also the term used in the 2008 Amendment to the UK Clinical Trial Regulations which permits waivers in emergency research trials on children[324]. It should be made clear that it is only appropriate to defer the authority of consent (to the child's parents), not its temporality (i.e. a temporal meaning of defer as 'delay').

Fourthly, I call for greater clarity in using the language of practicability and feasibility, and that this does not obviate the need for the individual checks of the physician-researcher role. With respect to this, I note the UK legislation refers to what is 'reasonably practicable'[325,326]. This may be preferable to referring to practicability or feasibility alone (as in US EFIC Regs) since it indicates the giving of a (person-specific) reason for proceeding without consent.

Finally, I suggest that within the UK MCA Regulations, we should re-state that mental capacity in emergency research is presumed unless shown otherwise. This is again to clarify that individual checks remain important despite the context of the research.

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[323] See also the full discussion of this in Chapter 3, Section 2.1)
[324] Medicines for Human Use (Clinical Trials) and Blood Safety and Quality Amendment (No.3) Regulations 2008. Statutory Instrument 2008 No 941. http://www.legislation.gov.uk/uksi/2008/941/contents/made. Accessed 19 April 2019.
[325] Mental Capacity Act 2005 (c. 9) (2005). Part 1, Research, Section 32(8)(b)
[326] Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006. Statutory Instrument 2006 No 2984. 2006. http://www.legislation.gov.uk/uksi/2006/2984/contents/made. Accessed 19 April 2019. (6)(b)

Chapter 6: Thesis conclusions and policy implications for justified decision-making in emergency research

Returning to my research questions

In the introductory chapter (Chapter 1), I firstly gave a background context to the doctoral research, stressing the essential tension between regulatory norms of research ethics governance and regulation, and permitting emergency research. I noted that emergency research poses a significant challenge to a regulatory model of research ethics, and its reliance on prospective written informed consent. Although emergency research is one among a number of types of medical research where the possibility of consent is unclear, its characteristics and the issues it raises are intractable using the current regulatory model of research ethics. I also clarified that the focus in my thesis was to justify the making of decisions about the ethics of emergency research. This focuses on justifying the processes, roles and operations which weigh the ethics of emergency research in particular instances.

Secondly, I defined emergency research and gave the rationale for my choice of case studies and focus on the US EFIC Regulations as the more demanding justificatory challenge to address in the research. I also defined the physician-researcher and her unique positionality and responsibility with respect to emergency research of therapeutic design. This was in preparation for thinking about a role for the physician-researcher in ethical decision-making at emergency patient enrolment.

Thirdly, I made a number of theoretical distinctions with a view to maintaining those distinctions in order to help the work of the thesis. These were:

1) the distinct roles of regulatory review and normal consent in the regulatory model of research ethics. Later in Chapter 3 having developed themes which mapped a critical landscape relevant to justifying decision-making, these became general and individual levels of decision-making, reflecting decision-making at regulatory review and participant enrolment respectively. Chapter 3 therefore showed the significance of the individual level of decision-making despite the absence of normal consent;

2) distinguishing the ethics of research from the ethics of research decision-making. The differences between the two justification endeavours are subtle, but important. As I showed in Chapter 4, questions of decision-making justification were premised on a particular account about the ethics of the research. Without being alive to this distinction, I would have limited the proper scope of analysis and arguments which should follow.

3) distinguishing justification and legitimacy in the thesis. While I focused on justification as the type of argument suited to my research approach I also used empirical components to legitimate elements of the justification. Elements were found in my analysis of Chapter 4, and my own concluding justification.

Aided by such theoretical distinctions, the research questions to be answered were:

- Main question 1: What justifies research decision-making to permit emergency research?
- Sub question 1a: What comprises and justifies research decision-making at regulatory review?

- Sub question 1b: what comprises and justifies research decision-making at the point of enrolment where consent would usually be obtained? This is envisaging enrolment under a waiver of consent to the research in the majority of cases.
- Main question 2: Does the regulatory model of research ethics (based in governance and regulatory norms) accommodate a justification, or require a fundamental revision? For example, rethinking the structure of the model, and whether different deciders or decision-making processes are warranted.
- Sub question 2: what changes to emergency research regulations and guidance follow from a minor or fundamental revision of the regulatory model?

Below I shall demonstrate how I answered each question, locating key findings from within the work of subsequent thesis chapters. Where relevant, I shall also indicate how theoretical distinctions aided robustness of key findings.

1. Key Finding 1: mapping the territory using five decision-making themes

Chapters 2 and 3 (mapping and developing a decision-making landscape) were essential to describe the full scope of issues pertaining to decision-making in emergency research, and how incoming regulations had responded to those issues. I used them to map out the territory to be covered in answering Main question 1: what justifies research decision-making to permit emergency research?

In the case study section of Chapter 2 I illustrated how, pre emergency research regulations, researchers struggled to obtain normal consent (see Case 1: NINDS); made incoherent arguments for alternatives to normal consent (see 'deferred consent' and 'nondisagreement' concepts in Case 3: PEG-SOD); or tried to waive consent altogether (see Cases 2-4: ISIS, PEG-SOD and TROICA). I also discovered a public dimension to issues

via public censure of regulatory review for acting in a discretionary manner (see Case 3: PEG-SOD) [327].

In the regulations sections of Chapter 2, I described the emergency research regulations arising from the US, EU and UK as a response to these issues, and indicated their descriptive similarities in how they aimed to resolve them [328]. From these regulations I drew three common themes pertinent to the question of decision-making justification in the thesis:

1) presuming waiving consent is permissible; 2) ensuring waiving consent is permissible; and 3) acceptability of risks and benefits.

Further I drew two additional themes from the US EFIC Regulations:

4) external and internal disclosures; and 5) community consultation.

By doing this, I established a focus within the thesis on justifying decision-making based on the requirements of US EFIC Regulations. This was in order to satisfy the more demanding justification challenge of those posed by the regulations I described, and in particular to explore the rationale for Themes 4 and 5, being unique to the US EFIC Regulations. In Chapter 3, I developed these themes more fully using conceptual analysis, and also examined a final case study (Case 5: Polyheme) for how it developed issues raising to Themes 4 and 5.

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[327] Chapter 2, Section 3
[328] Chapter 2, Sections 4-6

2. Key Finding 2: a reconciliation strategy underscores the emergency research regulations

I established that an apparent contradiction within the regulations – providing mechanisms for both the consent waiver and prospective consent – is actually a strategy to reconcile rule exception (consent waiver) with rule norm (consent). This strategy reflects general-level decision-making at regulatory review which presumes the waiver is permissible (Theme 1), coupled with individual-level decision-making at enrolment which ensures that the waiver is permissible (Theme 2). However, I noted this strategy risked an unintended influence of general- over individual-level decision-making, which side-lines the latter. This was indicative of how the regulatory model of research ethics, with its emphasis on norms like normal consent established by governance and regulation, fails in the absence of consent to give a rich conceptualisation of individual-level decision-making. (This finding also speaks to main question 2, suggesting the regulatory model of research ethics requires revision). I therefore took this strategy to indicate a potential role for individual-level decision-making at emergency enrolment, and to implicate the physician-researcher in the role, based on my discussion of her unique positionality to conduct ethical enrolment from Chapter 1 (see Chapter 1, Section 4 for this discussion).

In Chapters 4 and 5, I justified the two levels within this reconciliation strategy. In general, I showed the strategy is not incoherent but validates both obtaining and waiving consent where appropriate. Reason 1 in Chapter 4 reflects the general justification for the strategy:

> Reason 1: The reason of common purpose. Regulatory review secures commitment to a common purpose of ER under a waiver of consent, via a mixture of general and individual (delegated) decision-making. This reason presumes we have common interests in conducting ER. However, it does not oblige our participation in the research, as there is uncertainty about its risks and benefits. This motivates reliance within Reason 1 on delegated decision-making to ensure that commitment to the common purpose of the research is warranted in individual cases. This reason should be embodied in a real-world context through public disclosures prior to the research. These represent the accountability of the research to society.

Its delegated aspect looks to ensuring the waiver applies by individual-level decision-making. Key Finding 2 rebuts the claim that waiving consent in emergency research is 'a negation of accepted standards for clinical research' or does not add anything of justificatory value[329]. It also provides a solution to the struggles faced by researchers and regulators in the pre waiver era of regulation, who attempted unsuccessfully to maintain normal consent, and may have risked participant safety by so doing. Key Findings 3-6 speak to findings particular to the justification of decision-making at the general level of regulatory review, and the individual level of participant enrolment. They correspond to sub-questions 1a and 1b of Main question 1.

3. Key Finding 3: the minimal risk threshold should be replaced by a reason of reasonable risk

This key finding corresponds to sub-question 1a about what (specifically) justifies research decision-making at regulatory review, in addition to the general reconciliation strategy described above. In Chapter 3, I noted variation between the regulations about the acceptability and applicability of minimal risk in decision-making. In particular, the US EFIC Regulations, regulating 'higher risk' research of investigational novel drugs or

[329] Tigard, D. (2016). "Emergency Preservation and Resuscitation Trial: A Philosophical Justification for Non-Voluntary Enrollment." Bioethics 30(5): 344-352. p348

devices, were criticised for not having a minimal risk standard, and not disaggregating risk types in morally appropriate ways. However, my analysis in Chapter 4 found that the minimal risk threshold is inappropriate to decide meaningfully about risk.

Firstly, it cannot appropriately accommodate the range of emergency research therapeutic designs which we should decide about, in particular research on novel therapeutics. Secondly, it does not facilitate decision-making about risk, given persistent problems with how to disaggregate risk types and calculate minimal risk only with respect to nontherapeutic research procedures. Instead it seems the threshold either prevents the research or permits it only with a suboptimal design, which is liable to yield inaccurate or inadequately generalizable data. In this respect, in research jurisdictions where only one set of regulations contains a minimal risk threshold (such as the US WIC Regulations), this attracts poor research and poor research decision-making. This is because overall regulations with a minimal risk threshold are less demanding with respect to other requirements. This causes studies to shoe-horn designs in order to meet the minimal risk threshold, causing issues of suboptimal design, and leaving other issues (such as participant exploitation or social injustice) unaddressed. The persistence of minimal risk in accounts in Chapter 4 (such as Account 2: Largent and Account 4: McRae & Weijer) shows how accounts given of the ethics of the research may limit the scope of questions we should address in thinking about its decision-making. Maintaining the theoretical distinction between the ethics of research and its decision-making therefore aided my analysis towards this key finding.

In summary, the minimal risk threshold does not offer appropriate protection of participants, and should be replaced by a set of criteria which decide whether risks are

reasonable. As a result, my analysis in Chapter 4 has resulted in Reason 2 which rejects the use of minimal risk in the US WIC, and EU Regulations:

> Reason 2: The reason of reasonable risks. Regulatory review may decide risks using a mixture of both procedural and substantive criteria. Procedurally decision-making about risk is justified by assessments of risks which are reasonable relative to certain factors. Substantive criteria appropriately constrain these procedural aspects. This justification supports the concept of 'reasonable risk' as opposed to 'minimal risk'.

Risk criteria assessed at regulatory review are complemented by a specific check (counting as a supportive empirical component) that the research is reasonable at the individual patient level (again part of delegated decision-making). Overall, this is a more meaningful way to decide about risks, and to grapple with issues in particular cases of research, rather than banning decision-making outright of research whose risks cannot come under the threshold. Key Finding 3 shows that protectionist or risk-based approaches to decision-making are evidence of limited characterisation of the issues which emergency research poses.

4. Key Finding 4: community consultation supports the decision-making justification, both at regulatory review and at enrolment

This key finding corresponds to sub-questions 1a and b (what specifically justifies regulatory review decision-making and enrolment decision-making). My analysis of the community consultation requirement in Chapter 4 has found it not to yield a justificatory reason for either decision making at regulatory review or at enrolment in its current form. Nevertheless, it plays two supporting roles: 1) it rehearses parts of the justification for decision-making at enrolment which I make in Chapter 5; and 2) it acknowledges and assesses the impact of the research on social injustice where this is a relevant ethical consideration in the decision-making. However, I have argued that deciding the

relevance of social injustice in particular cases should be a required part of decision-making and part of the justification. This motivates the alteration of the current form of the CC into a two-stage decision-making process, the first stage of which requires giving an account about social injustice and other relevant contextual factors in the communities involved. The second stage would be to hold an active consultation in the community when warranted. This reflects Reason 3 in Chapter 4:

> Reason 3: The reason of considering social injustice. Community Consultation is split into two stages. Firstly, researchers and regulatory review are required to discuss whether the research is envisaged to impact social injustice (positively or negatively) in their communities of interest. Secondly, if social injustice is found to be a relevant factor, an active consultation is held to bring to light issues of social injustice, in addition to other issues raised by the community. During the CC, researchers may actively rehearse future decision-making at enrolment, also with an eye to social factors.

That the active, community-facing part of the current CC requirement should continue to be a requirement in some cases is controversial. While it diminishes the requirements on researchers working under the US EFIC Regulations (since it is not required in every case), it extends requirements for active community consultation to other research jurisdictions, increasing resource costs. On this last point, I note that SED trends in target emergency research communities have to date only been claimed in the literature on US-based emergency research. This might lessen the argument for an altered form of CC to be adopted in the other regulatory jurisdictions (e.g. EU, UK)[330]. I also maintain that conceptual clarity over the CC and its role in emergency research will aid efficient resource use to fulfil the requirement.

[330] This is despite concerning reports at the time of writing (April 2019) about increased knife crime and hospital admissions in the UK. See https://www.bbc.co.uk/news/uk-42749089.

5. Key Finding 5: the physician-researcher and patient should play a central role in ethical decision-making

This key finding corresponds to sub-question 1b about what specifically justifies research decision-making at the point of enrolment. Within this finding, I argued that the physician-researcher who enrols the patient during the emergency is in a position to conduct ethical decision-making and secure respect for individual patients as persons. In doing this I have restored a key role for the physician-researcher in ethical decision-making. I have also restored some of the respect owed to patients as part of the substantive-ethical value of normal consent.

I detailed the justification for the physician-researcher role in Chapter 5. The role is consistent with the emergency research regulations whose 'participant-satisfied conditions' directly implicate individual-level decision-making in the justification. This role rehabilitates the physician-researcher and the patient as ethically-significant decision-making entities at enrolment. The physician-researcher role is not dissimilar to the role she would undertake in normal consent, where she and the patient together conduct decision-making, and the patient gives final authorisation. However, it is a richer conceptualisation of individual-level decision-making than normal consent, as part of the regulatory model of research ethics, allows for. This is because her role retains a similar positionality and orientation towards the patient as a person worthy of moral consideration in both treatment and research terms. However, the role is not justified by reason of her providing proxy consent or authorisation for him. Instead the role is 'authoritative', that is to say justified, in a number of different ways. Firstly, justification comes from the reconciliation strategy itself, and associated theoretical agreement to pursue the common purpose of the research under the waiver provided

individual checks of its permissibility occur. Secondly, the physician-researcher may have consulted the community and rehearsed her future decision-making role with them. Thirdly, when undertaking the role she expresses respect for the patient as a person, giving him individual consideration despite mental capacity limitations and the research context. Fourthly, she conducts herself with integrity as a physician intending therapeutic benefit to the patient, and also as a researcher pursuing scientific goals. Her ability to manage her dual physician-researcher role appropriately is justified procedurally by the monitoring that regulatory review undertakes of processes within the role (e.g. attempts at consent). Finally, an extra enrol or exclude step in this process further supports appropriate role management. Together, the elements of this role allow for a richer conceptualisation of ethical decision-making during the enrolment encounter.

This role is markedly different from the involvement of researchers in cases such as ISIS (see Chapter 2, Section 3.2) and HEAT PPCI (see Chapter 5, Section 2) who were implicitly or actively discouraged from moral consideration of participants at enrolment. My argument supports my initial claim in Chapter 1 that the physician-researcher is uniquely positioned to hold the role by virtue of being responsible for index life-saving procedures in the research, and so crucial therapeutic benefit decisions. However, the role is also emblematic of other clinicians with clinical and research responsibilities who may also carry out enrolment. It therefore may be held by another clinician or clinicians who share part of the responsibility for those crucial therapeutic benefit decisions.

A role for the patient is also restored in the sense that his individual moral status is respected, despite his incapacity and the life-threatening, urgent context. This finding

improves upon existing justifications for emergency research in the literature, which are confronted by the inability to respect the participant's autonomy, and so attempt to argue away his individuality by generalizing about his choices or welfare.

6. Key Finding 6: the focus on justification has highlighted where empirical components support arguments

This key finding is general to the justifications made. Overall, the focus on justification in the thesis has maintained clarity about my research approach, aiding analysis of arguments and development of my own justification for decision-making. It has also identified how empirical components function in arguments and where these may usefully support arguments.

Firstly, it has identified and assessed where arguments in the literature contain empirical components (see Chapter 4, Section 3, Accounts 1, 2, 4 and 5: Faden et al, Largent et al, McRae & Weijer, and Sheehan et al). Two accounts risked being incoherent through an unclear contribution of empirical components to their arguments (see Chapter 3, Section 3.2 Criticisms of Account 2, and Section 3.4 Criticisms of Account 4). I also observed that another account was potentially limited in meaningfulness at the real-world level by defending a justification without the use of empirical components. This gave insufficient direction about how the account and its model should be taken to operate in practice (see Chapter 3, Section 3.5 Criticisms of Account 5).

Secondly, the focus on justification has led me to include supportive empirical components in my own arguments. These components 'legitimate' justificatory reasons, based on a certain account of legitimacy as about actual acceptance of those reasons. In Chapter 4, I used disclosures to rehearse the theoretical agreement to the common purpose of emergency research, and to demonstrate its social accountability (see Key

Finding 2, Reason 1 above). My use of the reasonable person standard in Reason 2 of Chapter 4 also incorporated a supportive empirical check of the existence of objections at the individual level (see Key Finding 3, Reason 2 above). So too, my rationale for community consultation finds it to lend support to the justification for decision-making at regulatory review and individual enrolment. In cases where its active (second) stage is warranted, it may also increase the researchers' knowledge of the community, or *vice versa*, by discussion of social injustice or other relevant issues. This knowledge increase is, however, incidental to the supportive value provided by the context of the actual rehearsal and consultation. In Chapter 5, the additional decision-making step emphasising permissible exclusion (as well as enrolment) of the participant manages the perception that conflicts of interest are being handled. This is a deliberate emphasis on part of the thought process within the physician-researcher role: the step encourages deliberation of the patient's interests both within and outside the research (Chapter 5, Section 8.2, Objection 2 where I argue why this step is valuable and not tokenistic).

Thirdly, the added empirical components mark the striking of a balance in my research approach (theoretical and conceptual bioethics). This is between the strength and validity of arguments versus their practical appropriateness[331].

Key Policy Implications

In this section, I address what regulatory and policy implications follow in light of the justifications I have made (and in light of answering main research question 1). This section demonstrates that we should revise our thinking about research ethics when

[331] See Chapter 1, Section 8 Approach to Analysis

modelled from an ethics governance and regulation standpoint. This section provides an answer to main and sub question 2 (revisions required of the regulatory model)

7. Focus on the US EFIC Regulations nevertheless results in generalizable findings

By focusing on the US EFIC Regulations, I have addressed the more demanding challenge for justifying decision-making. This is because my arguments have extended to additional requirements in the US EFIC Regulations for external and internal disclosures about the research, and community consultation. Nevertheless, my arguments and the policy implications which follow are generalizable to other regulations discussed in the thesis, despite being focused on US EFIC. In particular, it appears there may be a role for public disclosures about the research in UK and EU Regulations (and in the US WIC Regulations). This is because they help to rehearse the theoretical agreement to the common purpose of emergency research, and to demonstrate its social accountability (this role is described in Reason 1 of Key Finding 2 above.) I also advocate a 2-stage, community consultation process, the first stage of which should be a required part of decision-making at regulatory review, with the second stage a requirement in certain cases.

8. The justified reconciliation strategy should be made clearer

It is difficult to legislate for a reconciliation strategy which depends on occupying a transitional space between two norms of research ethics. These norms are 1) the regulatory, consent-based, model of research ethics (as described in Chapter 1, in particular Section 5) and; 2) the systematic waiving of consent (provided the waiver's permissibility is ensured at the individual level) which is justified by my arguments. As my analysis has shown, it is too easy to settle on wholly presuming the waiver applies as

a way of normalising it. When the exception to the rule becomes the rule in this way, then ethical sensitivity is lost as to why it was exceptional in the first place. Therefore, it seems problematic and misplaced to add the strategy in a regulatory context, or to highlight it in existing sets of emergency research regulations. Nevertheless, it is important to outline in guidance and the ethics literature how parts of the strategy are operating. Further follow-on publications from this thesis will also go some way to publicising the strategy and informing relevant stakeholders. I also maintain that the strategy is clearer by removal of terminology such as deferred consent. Furthermore, it is appropriate to clarify other terms which may wrongly imply individual-level decision-making is surplus to requirements.

Making the strategy clearer will help ethics committees and researchers to implement emergency research regulations with greater confidence. Confidence is further enhanced by the existence of other persuasive accounts which call for radical reform of the regulatory model of research ethics[332], and by comparing the emergency research case with other cases of research ethics decision-making where waiving consent is also a necessity.

9. We should emphasize the importance of individual level decision-making and the role of the physician-researcher

It is important to raise the profile of individual-level decision-making in the literature, and possibly also in the regulations themselves, by reordering and re-emphasizing it within existing regulatory clauses. I have suggested in Chapter 5 how to

[332] See the Learning Health System as argued for by Faden and colleagues, and described in Chapter 4, Section 3.1.

reorder clauses of the US EFIC Regulations (see Chapter 5, Section 9 Chapter conclusion and policy implications). Other regulations discussed in Chapter 2 (see Chapter 2, Section 4) may also benefit from reordering or insertion of clauses about attempts at consent. Guidance (not regulation) should elaborate and emphasize that this role extends to decisions to exclude as well as include eligible patients.

The role of the physician-researcher in realizing the value of individual-level decision-making will be elaborated in follow-on publications from this thesis. My arguments for this role cohere with an increased focus on research integrity and trustworthiness of the research establishment, and also speak to the literature around resolving moral distress experienced by healthcare practitioners.

10. Two concluding thoughts about giving justifications and current thinking in research ethics

Applying a theoretical and conceptual bioethics approach to the work of the thesis has provided me with a useful abstraction from the practical complexity of applying ethical decision-making to emergency research. However, the development of my own arguments reflects how in formulating a justification to address a set of real-world issues, we already start to trigger a dynamic shift from reasons which do not require actual agreement towards reasons which to some extent rely on empirical components. I have observed a key example of this shift in analysing the frameworks used in accounts in Chapter 4 which play a dynamic role in signifying or emphasizing empirical components (see Chapter 4, Section 6.2 for more details). It behoves future scholars to apply frameworks with care. Importantly, at the point of a framework being 'applied' at the real-world level, it will often affect the original argument which it frames, doing work upon the argument such that empirical components are signified or introduced. These

components, if not considered with care, may have unintended or unsupportive effects upon original arguments.

My doctoral research has proposed major revision of the regulatory model of research ethics since it has disturbed a foundational pillar in its structure: normal consent. In addition to other justifications for altering or waiving normal consent, the pillar risks toppling altogether. This then is a fertile time to develop our thinking in research ethics towards a new ethics model of research governance or regulation in research with human participants. Such a model recognises the ethical significance of the individual level, but does not elevate it to a status where it crowds out our common interests and purposes towards a better society.

Appendix A: Example of search strings used

I used the following searches to identify cases of emergency research in the literature:

1. PubMed 2017 search, inputting the following search string into the Advanced Search dialogue box:

> Search ((((((("Emergency Service, Hospital"[Mesh]) OR "Intensive Care Units"[Mesh]) OR "Burn Units"[Mesh])) OR (intensive care unit* OR critical care unit* OR high dependency unit*)) OR (emergency department* OR emergency ward* OR emergency unit*)) OR (trauma department* OR trauma ward* OR trauma unit* OR trauma centre* OR trauma center*)) OR (emergency treatment* OR emergency therap* OR trauma treatment* OR trauma therap* OR "intensive care" OR "critical care")

2. Web of Science 2017 search, selecting the Advanced Search tab and inputting the following search string:

> TS=((myocardial infarction OR stroke)) AND TS=((emergency OR acute OR trauma)) AND TS=((random* OR trial)) .

I only searched the following index: Science Citation Index Expanded (SCI-EXPANDED) --1945-present. In 2018 I repeated the Web of Science search above. I refined results by 'Highly cited paper'. This yielded 826 results. Within this, I refined further by Hot papers (defined as highly cited but also recent papers). This yield 26 results.

3. In December 2017 and November 2018 I used the following search in Scopus to identify discussions of the emergency consent waiver or other requirements within the regulations:

> consent waiver* OR consent exception* OR (exception* AND "informed consent") AND efic OR "delayed consent" OR "deferred consent".

Also in November 2018, I used the following search in Scopus to identify practice and conceptual literature about the community consultation requirement:

> (TITLE-ABS-KEY (("community consultation" OR "community notification" OR "community disclosure" OR "community engagement" OR "public consultation" OR "public notification" OR "public disclosure" OR "public engagement")) AND TITLE-ABS-KEY ("emergency department*" OR "emergency setting*" OR "emergency research"))

This gave 85 results which I then refined manually.

Appendix B: Acronyms

CC	Community Consultation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DHHS	Department for Health and Human Services
EM	Emergency Medicine
ER	Emergency Research
EU	European Union
FDA	Food and Drug Administration
IND	Investigational New Drug
IRB	Institutional Review Board
MCA	Mental Capacity Act
MHRA	Medicines and Healthcare Regulatory Authority
OPRR	Office for Protection from Research Risks
REC	Research Ethics Committee
SED	Social and economic disadvantage
UK	United Kingdom
US	United States of America
US EFIC	The US Exception from the Requirement for Informed consent in Emergency Research Regulations
US WIC	The US Waiver of Informed Consent Regulations

Appendix C: Bibliography

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