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# A review of research ethics guidelines on payment of healthy volunteers

## Abstract

Background: Payment of healthy volunteers in medical research is a prevalent practice but is the subject of ethical debate. Although regulations to protect healthy volunteers exist, these regulations differ between countries. Few data are available on the disparities between countries regarding guidance on payment of healthy volunteers in medical research.

Methods: This study aims to analyse guidance regarding payment of healthy volunteers in medical research in different countries, to identify common characteristics and differences, and to assess whether these are ethically significant. To this end, we analysed policies and guidance documents on payment of medical research subjects in the 11 countries with the most clinical trials registered as of the 12th of December 2022.

Results: 41 guidelines addressing treatment of research participants were identified. Of these, only six mention healthy volunteers, none of which are legally binding. All guidance documents identified lack details, and none define key terms such as “undue inducement”.

Conclusions: Local research ethics committees (RECs) have a huge role in determining what payment is acceptable, but there is little guidance provided for them. This gives RECs the freedom to make context-specific decisions, but also leads to variation in the protection of research subjects. Based on these findings, we make the following recommendations: 1) More countries need guidelines addressing payment of healthy volunteers in medical research. 2) These guidelines need more details than are currently included. 3) RECs also need guidelines to aid them in context-specific decisions on payment of research participants.

## INTRODUCTION

Healthy volunteer participation in medical research trace back to early clinical trials, where pioneering efforts to test new interventions often lacked the ethical rigour observed today[1]. These trials highlighted the need for guidelines to safeguard participants' rights and well-being. Ethical research and practice have developed considerably, including significant advancements in informed consent processes to ensure participants fully understand a study's purpose, procedures, potential risks, and benefits.

Specifically concerning benefits, ensuring the ethical treatment of healthy volunteers necessitates careful consideration of payment. While remuneration for research subjects is a widespread practice, its ethical standing is a matter of contention[2], particularly in studies involving healthy volunteers unlikely to derive therapeutic benefits. Although some contend that compensating research subjects is inherently unethical[3], the prevailing consensus leans towards acceptability[4]. Advocates posit that payment serves

as a means to recognise participants' investment of time, inconvenience, and exposure to potential risks. Furthermore, proponents argue that it is indispensable for fostering equitable recruitment in clinical trials[5-7]. Conversely, a prominent ethical apprehension revolves around the notion that payment may exert undue influence[4, 8], potentially compromising participants' independent decision-making in research involvement. This concern raises questions about the willingness of individuals to thoroughly explore the risks and benefits of participation[9].

A review of the literature shows a scarcity of information on payment of participants in biomedical research. There is a heterogeneity of payment policies globally, encompassing varying guidelines and ambiguous terms in ethics literature. Ethical consensus on the appropriateness of compensation remains elusive, as scholars and regulatory bodies grapple with defining undue inducement and coercion. Firstly, Klitzman et al[10] highlight the dearth of information on payment in research articles, with a mere fraction mentioning financial remuneration. A Medline search covering diverse health conditions found that only 13.5% of 207 articles referred to financial remuneration, indicating a significant information gap in the discourse.

Secondly, the literature evidences a global variability of payment-related policies and practices. This diversity is exacerbated by vague terms in bioethics literature and international guidelines, further complicating the ethical dimensions of payment[11]. For example, The Declaration of Helsinki (DoH) does not address payment directly and only mentions that information on “incentives for subjects” must be included in the study protocol[12]. Regulatory guidance in the US and the EU offers limited insights, resulting in substantial disparities in local payment policies[2, 13-18]. Substantial disagreement and confusion also prevail among Institutional Review Boards (IRBs), investigators, sponsors, bioethicists, and research participants as to what constitutes an excessive payment[15, 19-21]. This lack of consensus extends to the assessment of risk-based payments, further confounding ethical decisions[13-15, 19-21].

Despite the widespread practice of compensating healthy volunteers in research, the discord surrounding its acceptability and operationalisation, and with the divergences in regulations and guidance across various nations, a comprehensive examination is notably absent. To date, no study has systematically scrutinised national and international guidance documents to gauge their treatment of these critical issues. This review aims to fill this gap by analysing guidance documents from countries with the highest clinical research output. This study seeks to serve as a foundational examination, paving the way for an insightful discussion on the intersection of guidance and the ethical discourse surrounding the payment of healthy volunteers in medical research.

## METHODS

The protocol for this study was preregistered on Open Science Framework prior to any data being collected[22].

### data collection

Two of the authors independently searched for guidelines or regulations addressing the payment of non-patient research participants in medical research in the 11 countries with the most clinical trials registered on the World Health Organizations' International Clinical Trials Registry Platform on the 12th of December 2022 (Table 1) [23].

| Country | Number of Clinical Trials |
|---|---|
| United States of America | 168924 |
| China | 77204 |
| Japan | 61404 |
| Germany | 51692 |
| India | 50284 |
| United Kingdom | 46832 |
| France | 43124 |
| Canada | 33968 |
| Iran | 33674 |
| Spain | 31517 |
| Australia | 31275 |

*Table 1 Clinical Trials Registered by Country*

Search results were limited to sources published after 2000 to reflect current practices, and to documents available in English. Inclusion and exclusion criteria are detailed in Table 2. Searches were begun in December 2022 and completed in September 2023.

Searches were conducted across three databases: NIH ClinRegs, an online database of clinical research regulatory information; Overton, the largest online database of international policy documents; and a targeted Google search.

NIH ClinRegs was searched for guidelines of the countries selected using the following protocol.

1) Search the page for "payment"
2) Review all guidance/regulatory documents mentioned in the identified section against the inclusion criteria.
3) Review all guidance/regulatory documents mentioned in the "Insurance and Compensation" section against the inclusion criteria.
4) Review all guidance/regulatory documents mentioned in the "Informed consent > Required elements" section against the inclusion criteria.
5) Search the page for the following terms and review all guidance/regulatory documents mentioned in the identified sections against the inclusion criteria.
    a. "reimb"
    b. "compens"
    c. "incentive"

Overton was systematically searched as follows:

(payment OR remuneration OR "financial compensation" OR reimbursement OR "financial incentive") AND (volunteer OR "research subject" OR "research participant") AND (“medical research” OR “clinical research”) AND (guidance OR guideline* OR regulation*)

Google was searched using the following protocol:

1) Open private search tab
2) Search “country” regulations for clinical trials
3) Open first 50 pages
    a. If page addresses regulations or guidance for medical research: Look for mention of guidance or regulatory documents
        i. Search for “act”, “law”, “guid” and “regulat”
        ii. If there is a mention, search Google for document
4) Search “country” guidance for clinical trials
    a. If page addresses regulations or guidance for medical research: Look for mention of guidance or regulatory documents
        i. Search for “act”, “law”, “guid” and “regulat”
        ii. If there is a mention, search Google for document
5) Within documents, search for
    a. “Financ”
    b. “Reimb”
    c. “Incent”
    d. “Compens”
    e. “Expense”
    f. “Payment”

| **Inclusion criteria** | **Exclusion criteria** |
|---|---|
| 1) Published after 2000<br>2) Currently valid<br>3) Address the payment, recruitment, or involvement of research participants in medical research<br>4) Developed by any national organisation of the countries included<br>5) Available in English | 1) Published before 2000<br>2) Not currently valid<br>3) Not available in English |

*Table 2 Inclusion and Exclusion Criteria*

Additionally we decided to exclude guidelines that focus solely on the inclusion of children in research. Within the law, a large number of rules and regulations apply to children exclusively due to additional concerns for safeguarding, and physical and mental maturity. These are beyond the scope of this review.

Documents that solely cited or referred to a main document without providing a further interpretation or application of the document were not considered in this review.

**review and analysis of data**

Both reviewers then filtered for documents of the "Clinical guidance" type, documents published after 2000, and excluded documents published by individual NHS trusts. Titles of identified documents for the countries of interest were reviewed and relevant documents were screened. The PRISMA flow diagram[24] for the study can be found in Figure 1.

*Figure 1 Adapted PRISMA 2020 flow diagram*

All documents were reviewed by two independent reviewers. Conflicts between reviewers were resolved by discussion. There were no cases where consensus could not be achieved.

Data was then retrieved from identified documents using a data collection form. The data collection form was designed to include aspects highlighted in the ethical literature, as referenced in Box 1.

Does the guidance specifically address the payment of healthy volunteers?[7, 25-27]

Does the guidance recommend the payment of participants in research generally?

Are certain circumstances listed in which paying healthy volunteers is recommended or not recommended?

Does the guidance recommend that information on payment for participating in the trial is included in information provided to participants?[7, 9, 28-31]

Does the guidance recommend that a number of anticipated payment is included in the information provided to participants? [7, 9, 28-31]

Does the guidance recommend that payment is listed as one of the potential benefits of taking part?[32-34]

Does the guidance mention that a sum shouldn't be excessive?[5, 8, 14, 20]

Does the guidance elaborate on how to determine an appropriate amount of payment?[5, 35, 36]

Does the guidance recommend that information on payment of participants over and above expenses incurred be included in the ethics committee submission?[4, 15, 20, 37, 38]

Does the guidance recommend that ethics committees critically review the payment of participants (e.g. make suggestions on appropriate amounts)?[4]

Does the guidance recommend that members of the ethics committee receive training in scientific research ethics?[37, 38]

*Box 2 Ethical aspects identified in literature search*

## RESULTS

Of the 11 countries reviewed, relevant results were found for eight countries (USA, UK, Australia, Canada, India, Germany, Spain, Japan) as well as international organisations they were part of and had adopted guidelines from (e.g. EU, International Conference on Harmonisation). Documents from France, China and Iran were not available in English. The data is available in Supplementary Table 1[Supplementary File 1]. Excluded documents are listed in Appendix A[Supplementary File 2]. Documents cited are referenced in the Supplementary Bibliography[Supplementary File 3].

What is most notable from the review is that 41 guidelines (Table 3) were found of which only six (s1-s6) specifically mentioned payment for healthy volunteers.

| Country | Guidelines |
|---|---|
| Australia | Payment of Participants in Research: Information for Researchers, HRECs and Other Ethics Review Bodies. 2019.(s1)<br>National Statement on Ethical Conduct in Human Research. 2007. (s7)<br>National Standard Operating Procedures for Clinical Trials, including Teletrials, in Australia. 2021. (s8) |
| Canada | Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 2022. (s2)<br>Research Ethics Board: Overview of the Health Canada and Public Health Agency of Canada REB. 2023. (s9)<br>Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications. 2013. (s10)<br>Research Ethics Board's Operational Policy Framework. 2010. (s11) |
| EU | The rules governing medicinal products in the European Union, Volume 10, Part II Document Harmonisation Guidance. 2020. (s12)<br>Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. 2017. (s13)<br>Regulation (EU) 2017/745 of the European Parliament and of the Council. 2017. (s14)<br>Directive 2001/20/EC of the European Parliament and of the Council 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. 2001. (s15)<br>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. 2014. (s16) |
| Germany | Ordinance on the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for use in humans. 2004. (s17) |
| India | New Drugs and Clinical Trials Rules. 2019. (s18)<br>Handbook for Applicants & Reviewers of Clinical Trials of New Drugs in India. 2017. (s19)<br>Pre-Screening Checklist for Clinical Trial and New Drugs Applications. 2015. (s20)<br>National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. 2017. (s21)<br>Handbook: National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. 2018. (s22)<br>GCP Inspection Checklist. 2018. (s23)<br>The Drugs and Cosmetics Act and Rules. 1940 (updated 2016) (s24) |

| | |
|---|---|
| International | International Ethical Guidelines for Health-related Research Involving Humans, Fourth edition. 2016. (s25)<br>WHO Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation. 2005. (s26)<br>Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). 2016. (s27) |
| Japan | Clinical Trials Act (Act No. 16 of April 14, 2017). 2017. (s28)<br>Ministerial Ordinance on Good Clinical Practice for Drugs. 2022. (s29) |
| Spain | Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry. 2015. (s30)<br>Memorandum on Collaboration and Exchange of Information between the Spanish Agency of Medicinal Products and Medical Devices and Ethics Committees for investigation with medicinal products. 2018. (s31)<br>Instruction document of the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain. 2021. (s32)<br>Annex VIIIA: Guideline for correct preparation of a model patient information sheet and informed consent form (PIS/ICF). 2021. (s33) |
| UK | Insurance and Compensation in the Event of Injury in Phase 1 Clinical Trials. 2012. (s3)<br>HRA Guidance: Payments and Incentives in Research. 2014. (s4)<br>Guidelines for Phase 1 Clinical Trials: 2018 Edition. 2018. (s5)<br>Medicines for Human Use (Clinical Trials) Regulations. 2004. (s34)<br>Standard Operating Procedures for Research Ethics Committees. 2022. (s35)<br>Consent and Participant Information Guidance. 2021. (s36)<br>Research Governance Framework for Health and Social Care. 2005. (s37)<br>Guidelines on the practice of ethics committees in medical research with human participants: Fourth edition. 2007. (s6) |
| USA | Information Sheet: Payment and Reimbursement to Research Subjects - Guidance for Institutional Review Boards and Clinical Investigators. 2018. (s38)<br>45 CFR Part 46 Subpart A. 2017. (s39)<br>Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors. 2023. (s40)<br>Code of Federal Regulations, Title 21, Part 50: Protection of Human Subjects. 2022. (s41) |

*Table 3 Regulations and guidance documents identified*

For India, the National Ethical Guidelines for Biomedical and Health Research (s21) acknowledged the need for special consideration for healthy volunteers without providing specific details. Emphasising the prevention of volunteers participating in multiple studies via registries, the guidelines underscored the importance of vigilance in participant recruitment.

Within the United Kingdom, four distinct documents(s3-s6) touched upon healthy volunteers, yet none held binding status. Recommendations ranged from compensating for non-therapeutic phase I trials, as suggested by the Association of the British Pharmaceutical Industry (ABPI) guidelines(s3), to a stance by the Health Research Authority (HRA)(s4) allowing for both compensated and non-compensated scenarios. ABPI further outlined payment structures based on minimum hourly wage, with additional provisions for discomfort.

Canada's Tri-Council Policy Statement(s2) highlighted the significance of incentives in safeguarding the voluntariness of participation, particularly concerning healthy volunteers. It stressed the need to mitigate therapeutic misconception, emphasising that participants should not accept risks they would not otherwise consider due to financial incentives.

Australia's Payment of Participants in Research guidelines(s1) took a distinctive stance by actively discouraging payment. However, it acknowledged circumstances where payment, limited to reimbursement for expenses and remuneration for time and inconvenience could serve as an incentive for early-phase clinical trials, provided adequate processes were in place.

Despite these insights, it is crucial to note that all identified guidelines, regardless of the country, lacked specific details. None provided explicit definitions for crucial terms such as "undue inducement," with the term "no undue influence" mentioned in ten guidelines(s1, s2, s11, s12, s14, s16, s21, s25-s27) without a clear consensus on the definition.

Moreover, the prevailing content of the guidance documents was characterised by a lack of a definitive stance on payment of research participants, particularly in the case of healthy volunteers. Australia's guidelines(s1) notably discouraged payment, while others deemed it "acceptable"(s4, s6, s33, s38, s40). A subset (s3, s16, s24, s29, s37) exclusively addressed compensation concerning injury. There was an apparent consensus that any payments should not confer a benefit, as explicitly stated in only three guidelines(s26, s38, s40)
Additionally, 22 out of 41 guidelines explicitly specified that anticipated payment should be outlined in informed consent (s1-s9, s18, s21-s27, s33, s36, s38-s40). However, only three guidelines(s1, s5, s25) provided specific details on determining an appropriate amount, citing minimum wage standards.

Another notable finding was the lack of differentiation in financial considerations for participants between reimbursement for expenses and compensation for time or inconvenience. Nine(s1, s5, s6, s17, s22, s25, s27, s32, s35) out of 20(s1, s2, s5, s6, s11, s12, s15, s17, s21, s22, s25-s27, s30-s32, s34, s35, s38, s40) guidelines that mentioned financial considerations in ethics committee submissions did not distinguish between these two forms of payment.

Finally, the necessity of at least one research ethics committee member with training in research ethics was specified in only seven guidelines(s7, s10, s11, s21, s22, s24, s25, s30), highlighting a potential area for improvement in ethical oversight.

## DISCUSSION

The results of this review shed light on critical gaps and challenges in the current landscape of guidelines addressing the payment of research participants, particularly healthy volunteers. The findings underscore the need for comprehensive and nuanced considerations to ensure ethical practices in the remuneration of individuals contributing to medical research.

### enforceability

One significant finding is the predominant reliance on guidelines rather than legally binding regulations to address payment practices. This poses a potential challenge to enforceability[39] and raises questions about the consistency of recommendations across various jurisdictions. Notably, the lack of international consensus on the status of guidelines, exemplified by the disparity between Australian(s7) and Canadian(s10) guidance, further complicates the regulatory landscape.

### lack of clarity and inconsistencies

A noteworthy observation is the reluctance of existing guidelines to take a clear ethical stance on payment of research participants. This ambiguity is particularly evident in the lack of definitive recommendations, either in favour of or against payment. Additionally, the lack of clarity on the threshold for incentives before they constitute undue influence remains a significant ethical challenge.

The study also reveals the lack of consensus and consistent standards among Institutional Review Boards (IRBs) and RECs, emphasising the need for standardised definitions and criteria. The struggle to define terms like "coercion" and "undue influence" based on subjective judgments underscores the urgency of establishing clearer ethical parameters within the research community.

An unresolved issue is the lack of agreement, both in the literature and global guidance, on whether payment can constitute undue influence. This raises critical questions about the ethical implications of financial incentives. The influence of higher payment on the willingness to participate, as illustrated by Bentley and Thacker's study[9], underscores the need for a more nuanced understanding of the interplay between payment and participant decision-making processes.

### role of RECs and IRBs

The pivotal role of RECs and IRBs in determining the acceptability and ethicality of payment emerges as a crucial point of consideration. However, the lack of specific guidance for these committees limits their effectiveness. The absence of guidance on what constitutes an effective IRB or REC, coupled with the dearth of a standardised process or methodology for their evaluations, calls for a re-evaluation of the support structures in place.

### could a lack of consensus be an advantage?

The paucity of detail and inconstancies in existing guidelines could arguably be considered advantageous. For example, some may consider that the existing research ethics infrastructure allows researchers, RECs and IRBs flexibility to tailor payment structures to specific contexts. Furthermore, it may be considered infeasible to institute and ensure governance that guarantees standardisation for healthy volunteers internationally.

Nevertheless, the findings of this review underscore a pervasive lack of guidance, regulatory consensus, and even a fundamental agreement on the threshold at which incentives may constitute undue influence. This deficiency poses a significant compromise to the protection of research participants, emphasizing the imperative for extensive ethical research and thoughtful deliberation. Such efforts are essential to formulate practices that are not only locally adaptable but also globally comparative, ensuring a robust ethical framework in diverse research contexts.

## recommendations

In light of these gaps and challenges, several key recommendations emerge:

- Expansion of Guidelines: More countries should establish guidelines addressing payment of research participants, particularly healthy volunteers.

- Enhancement of Guideline Details: Guidelines should have more explicit details, including clear distinctions between reimbursement and compensation for time and inconvenience, criteria for determining appropriate amounts, and the specific information to be provided to participants.

- Guidance for RECs and IRBs: Comprehensive guidelines should be developed specifically for RECs and IRBs, outlining their roles, necessary expertise, and standardised evaluation processes.

- Standardised Definitions and Criteria: There should be an establishment of consistent standards and definitions, particularly concerning terms like "coercion" and "undue influence."

- International Collaboration: International collaboration should be established to develop a consensus on the ethical considerations surrounding payment, fostering a more cohesive approach across borders.

## limitations

This review's main limitation is found within the systems within which the law operates and the assumptions that we, the authors, had made about it. We had a-priori introduced the exclusion criterion that documents had to have been published or formally revised after the year 2000 to ensure that only current legal documents operating within modern research systems were included. Due to this, two documents (s42, s43) were excluded that are still considered legally valid.

Further, we cannot claim to provide a comprehensive overview of all relevant legal documents of all countries that have been examined in this review, nor does our review reflect how the documents identified for each country fit into their respective wider legal framework or are applied in practice.
Lastly, the documents of the countries China, France, and Iran were only available in the official languages of the countries and therefore inaccessible to us. We have yet provided the identified documents in our exclusion list so that this work can be continued by scholars who can claim a substantive understanding of the jurisprudence and language of these countries.

## CONCLUSION

This review highlights that compensating research participants remains a complex ethical challenge, characterised by heterogeneity in practices and conflicting viewpoints. The review reveals the need for harmonising global payment policies, addressing undue inducement concerns, and fostering transparent communication among researchers, ethics committees, and participants. Achieving an ethical balance between motivating participation and safeguarding participant autonomy requires ongoing interdisciplinary dialogue and regulatory clarity.

**Figure Legends**
Figure 1: Adapted PRISMA 2020 flow diagram

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