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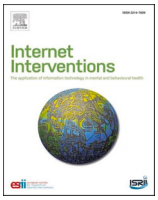

Ethical review procedures in international internet-based intervention studies

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ABSTRACT

International internet-based studies could be accessible by participants from various countries worldwide. However, the jurisdiction of research ethics committees (RECs) or institutional review boards (IRBs) is bound to geographical state or country borders. How can researchers deal with the geographical boundaries in the jurisdiction of RECs/IRBs versus the worldwide, open character of international internet-based research? Should ethical approval be sought in each country where participants will be recruited? In this paper, we want to share our challenges in setting up the ethical review procedures in an international internet-based mHealth intervention study, to further the discussion on ethical procedures in internet-based research.

1. Introduction

Internet-based research uses data directly available on the internet (e.g., comments on online community platforms, the number of likes on Instagram) or uses the internet as a way to approach potential research participants and collect online (survey) data (National Committee for Research Ethics in the Social Sciences and Humanities, 2014). Whereas international internet-based studies could be accessible by participants from various countries worldwide, the jurisdiction of research ethics committees (RECs) and institutional review boards (IRBs; in the USA) is bound to geographical state or country borders (Harriman and Patel, 2014). This is an important issue that was raised in 2014 by Harriman and Patel, and is still a highly relevant challenge. How can researchers deal with the geographical boundaries in the jurisdiction of RECs or IRBs versus the worldwide, open character of international internet-based research? Should ethical approval be sought in each country where participants will be recruited?

Some RECs and IRBs have created guidelines specifically for internet-based research, for example the Norwegian National Research ethics committees released 'A guide to internet research ethics' (National Committee for Research Ethics in the Social Sciences and Humanities, 2019) in which they highlight important ethical issues such as the discussion whether data on the internet is public or private, or whether informed consent should be obtained. In 2013, the US Department of Health and Human Services (HHS) released a document with considerations regarding human subjects in internet-based research (Secretary's Advisory Committee on Human Research Protections, 2013). This document illustrates the diversity in legal jurisdiction regarding internet-based research depending on state, national or international laws and regulations, and is mainly restricted to internet-based research in the USA (Clark et al., 2019). These guidelines, however, did not explicitly state which REC(s) should be consulted for ethical review procedures in internet-based research that recruits participants on the World Wide Web. Also, the Association of Internet Researchers (AoIR), which incorporates an Ethics Working Committee of international ethicists and researchers aiming to ensure that 'research on and about the Internet is conducted in an ethical and professional manner' (Association of Internet Researchers, n.d.), does not provide information about the ethical approval procedures in case of international internet-based research. The European Network of Research Ethics Committees (EUREC) only provides information regarding EU legislation for *onsite clinical trials on medicinal products* for human use, stating that in a multinational multi-centre trial, an ethical opinion of a REC in each participating country would be required (European Network of Research Ethics Committee, 2012). A European initiative on other types of clinical research than clinical drug trials, such as observational, survey or psychosocial or behavioral intervention studies is lacking (Veerus et al., 2014). Obviously, there is a difference between onsite studies distributing medicinal products by care professionals and studies delivering online surveys or behavioral interventions.

2. Our case: an international mHealth intervention study

We encountered the question on the geographical jurisdiction of RECs/IRBs in international internet-based research when we were setting up an international randomized controlled trial (RCT) testing the effectiveness of a self-management mobile application (the *Untire app*) in reducing fatigue and improving quality of life in patients with cancer and survivors (Spahrkäs et al., 2020). The study planned to recruit participants from seven countries (Australia, Canada, Germany, the Netherlands, Spain, the United Kingdom, and the United States of America) via advertisement campaigns on Facebook and Instagram

Abbreviations: REC, research ethics committee; IRB, institutional review boards.

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(Spahrkäs et al., 2021). The recruitment, study assessments, as well as the randomization to either the intervention condition in which participants received immediate access to the Untire app or the waiting-list control condition, took place online. We encountered two questions in applying for ethical approval in this international internet-based study, and at that point in time (2017), very limited international mHealth intervention studies were published that we could learn from. Therefore, we want to share our experiences to further the discussion on ethical procedures in internet-based research.

2.1. Challenge 1

Question 1: A research team of one research institute is conducting an internet-based study, targeting participants via online social media advertising campaigns in several countries. The research team is solely responsible for recruiting participants, sending out online questionnaires, offering the intervention, and the storage and analyses of the research data. From an ethical standpoint, would this international internet-based study be considered a single site or a multisite trial? In other words, would it be considered good clinical practice to obtain only an ethical opinion at the REC of the institute of the principal investigator, or are ethical opinions needed in each country targeted in the study?

We searched online for official directories or guidelines, explored the existing literature for examples of international internet-based intervention studies, and consulted the REC of our institute. First, we failed to find directives or guidelines regarding ethical approval procedures in international internet-based intervention studies, as shown above.

Secondly, we explored the literature for examples of international internet-based intervention studies. We found only one example: a pilot RCT in which an online self-help intervention for postpartum depression was offered via Google advertisement to pregnant female internet users worldwide (Barrera et al., 2015). This study recruited women from 23 countries, and the procedure and materials were approved by two university institutional review board committees in California, the USA. Given the lack of international internet-based intervention studies, we searched for examples of international *onsite* intervention studies. We found two examples: in one study, intervention participants with diabetes type two received the drug fenofibrate in one of the 11 participating clinical centres in four countries, and in the other study, intervention participants were randomized into a 2 × 2 diet and physical activity intervention offered by one of the eight institutions in eight countries. Both studies applied for and received ethical approval from the ethics committee of each of the participating institutions. When we searched for international studies that include physical measurements or physical visits (e.g. to take a venous blood sample, to conduct an interview), we found that a local ethic review board in each of the participating countries approved the study (Thanopoulou et al., 2003; Vancampfort et al., 2018). However, when we searched for international *internet-based survey* studies, we found two examples in which researchers applied for and received ethical approval only by the REC of the principal investigator (PI), even though participants in multiple countries were recruited (DiBonaventura et al., 2010; Hämeen-Anttila et al., 2014). Another international *internet-based survey* study recruited participants worldwide but applied for ethical approval at the research institutes of all participating researchers, i.e. in the United Kingdom and the United States of America (Davis et al., 2021). Based on the available examples, it seems that when multiple institutions in several countries were physically involved, researchers applied for ethical review at each institution. However, when international survey or intervention studies took place entirely online, researchers only applied for ethical review at the ethical review committee of the researchers' institute.

Thirdly, we consulted the REC of our institute and learned that this was the first international internet-based study they reviewed. In our case, the REC of our host institute granted a favourable opinion explicitly for recruiting participants in the Netherlands and advised us to seek for ethical review procedures in each country targeted in our study, just to be sure. This brings us to the second question.

Table 1
The various routes for applying for ethical review procedures in an international internet-based mHealth intervention study.

Ethical approval needed?	Country	Contacted institute for ethical approval	REC contacted by	Comment on the ethical procedure needed
Yes	NL	Medical Ethics Review Board at institute of researchers	Directly accessible by the researchers	Full review procedures were needed to recruit participants in the Netherlands.
	GER	National society	Application possible by a researcher, but needs to be in German	Full review procedure.
	ESP	University REC	Application only possible involving a member of the university	Full review procedure.
	UK	University REC	Application only possible involving a member of the university	Full review procedure.
No	USA	Governmental institute	The researchers directly contacted the institute	The governmental institute exempted this study from ethical approval.
	CAN	Governmental institute	The researchers directly contacted the institute	The study is not funded nor hosted in Canada, therefore Canadian national authorities do not need to review this study ethically.
	AUS	University REC	The researchers directly contacted the university	The Research Ethics and Compliance department of the university stated that the ethical approval of the UMCG is sufficient and no further ethical procedures are needed.

Note: REC = research ethics committee; NL = the Netherlands; GER = Germany; ESP = Spain; UK = the United Kingdom; USA = the United Stated of America; CAN = Canada; AUS = Australia.

2.2. Challenge 2

Question 2: In case researchers aim for ethical review procedures in the countries targeted in an internet-based study, where do researchers apply for ethical review?

An advantage of internet-based research is that a research team at a certain geographical location can efficiently conduct a worldwide international study. This could even be done without collaborating with international colleagues. However, when only one institute is involved in conducting the international internet-based study, where does a researcher apply for ethical review in each country?

We searched online for information about official ethical procedures in the targeted countries, and we asked our colleagues working in those countries for information. The organisation of ethical committees varies

among countries, with countries having a national central REC system, a regional RECs system, or independent or institutional RECs (Walanj, 2014). The information found online and advice from international colleagues resulted in various routes to obtain ethical approval in the different countries, which are displayed in Table 1. In our case, some governmental institutes qualified to make statements about ethical review procedures exempted the study from ethical review (the USA and Canada). The route via colleagues working at universities resulted in full review procedures (Spain and the UK) or approval based on the ethical opinion of the PI's host REC (Australia). One national society provided approval after applying for full review procedures via a German colleague. Our approach resulted in statements of an official body about the ethical review procedures for this study in each country, ranging from exemption to a full review procedure.

3. Conclusion

We believe that upon today, researchers conducting international internet-based research encounter the contraction between the legal jurisdiction of RECs or IRBs using state or country borders and the worldwide potential of internet-based research. Based on the guidelines and examples so far, it seems obvious for researchers to approach ethical review committees of participating institutes in international studies when physical activities are involved, such as providing study drugs or taking a blood sample. However, for international internet-based studies that take place solely online, it seems less obvious to apply for ethical review procedures in multiple countries. Whether this is ethically solid still needs to be answered. Therefore, ethical guidelines on which, and how, RECs or IRBs need to be approached in international internet-based research are very welcome. In addition, it would be valuable that RECs or IRBs review several ethical issues specifically related to internet-based intervention studies, for example on how participants will be supported during the intervention and follow-up (Harriman and Patel, 2014), or on who will guard participants' safety in case of deterioration due to the intervention. We invite experts on this topic to provide guidelines to facilitate researchers in conducting their studies in line with good clinical and ethical practice. We can imagine that a simple answer could not be provided. Still, we need to strive towards more guidance on this topic, especially since many international internet-based studies take place now and in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

No data was collected for writing this manuscript.

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