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Review

Emergency research without prior consent in the United States, Canada, European Union and United Kingdom: How regulatory differences affect study design and implementation in cardiac arrest trials

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Abstract

Aim: A major barrier to performing cardiac arrest trials is the requirement for prospective informed consent, which is often infeasible during individual medical emergencies. In an effort to improve outcomes, some governments have adopted legislation permitting research without prior consent (RWPC) in these circumstances. We aimed to outline key differences between legislation in four Western locations and explore the effects of these differences on trial design and implementation in cardiac arrest research.

Data sources: We performed a narrative review of RWPC legislation in the United States (US), Canada, the European Union (EU) and the United Kingdom (UK).

Results: The primary criteria required to perform RWPC was similar across locations: the study must involve an individual medical emergency during which neither the prospective subject nor their authorized representative can provide informed consent. The US regulations were unique in their requirements for performing Community Consultation and Public Disclosure in the communities in which the research takes place. Another major difference was the requirement for consent for ongoing participation in Canada, the EU and the UK, while only notification of enrollment and the opportunity to discontinue participation are required in the US. Additionally, only Canada and the EU explicitly state that the subject or their representative may request withdrawal of their data.

Conclusion: Regulations governing RWPC in the US, Canada, the EU and the UK have similar goals and protections for vulnerable populations during medical emergencies. Differences in the qualifying criteria and implementation procedures exist across locations and may affect study design.

Keywords: Cardiac arrest, Clinical trials, Deferred consent, Exception from informed consent

Introduction

Cardiac arrest research suffers from a paucity of high-quality randomized clinical trials to inform best practices for resuscitation efforts, and as a result, the majority of international arrest guidelines rely heavily on observational data.[1,2] This can be attributed in part to the difficulty in conducting clinical trials for emergency medical conditions. Specifically, the key principle of obtaining informed consent prior to research participation[3] is often impossible during medical emergencies given the victim's lack of consciousness, the absence of a third-party authorized representative (AR) and/or significant time restraints related to the need for rapid intervention. As governing bodies worldwide have recognized the need for high quality research during medical emergencies, many have adopted regulations addressing the need for research without prior consent (RWPC). However, the RWPC legal framework varies between countries and unions in ways that may impact trial design and implementation.[4,5] Therefore, we performed a narrative review of the current legislation on RWPC in the United States (US),[6] Canada,[7] the European Union (EU)[8] and the United Kingdom (UK).[9,10] We aimed to outline key differences in each set of regulations and explore how these systems balance the added barriers to research with the protections of vulnerable patient populations in cardiac arrest trials.

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Search strategy

Publicly accessible official government websites for each country/union were searched for the most recent regulations on human subjects research. Sections pertaining to informed consent and RWPC were reviewed in English by at least two authors. Differences in the interpretation of the legislative text was discussed until consensus was reached by the author group. Additional literature relevant to the interpretation, implementation and effects of the requirements outlined in these regulations was included at the discretion of the author group for illustrative purposes.

It is important to note that *the legislation reviewed here is derived from national or supranational government bodies, but the states, territories, provinces or member countries within each country/union may have additional laws on the subject* which, for simplicity, will not be discussed in this review.[11,12] Additionally, the UK has separate regulations for RWPC that does not involve medicines (i.e. procedural and other non-medicinal interventions) which will not be reviewed here.[13]

Terminology

Throughout this document we discuss concepts which have significant overlap across the geographic locations of interest for which the local terminology differs. In some cases, these differences reflect true distinctions for a given concept. For instance, while the US and Canada are sovereign countries, the EU is a supranational political and economic union composed of 27 European countries and the UK is an asymmetrically decentralized unitary state, comprised of England, Scotland, Wales and Northern Ireland. For the purposes of this review, we will refer to them as "locations" or "countries/unions."

Another meaningful difference in terminology is that for RWPC itself. In the US, the process is called "Exception From Informed Consent" (EFIC) while Canada uses the official term "Exception to Consent," and the EU and UK legislative documents do not appear to cite a specific term. However, in Canada, the EU and the UK, investigators often refer to the process as "deferred consent."[12,14,15] Here, the difference in terminology reflects a divergence in practice: in the US, consent is waived during the medical emergency and the subject may remain in the study without additional consent unless they withdraw participation; in Canada, the EU and the UK, informed consent for ongoing participation must be obtained as soon as possible. It should also be noted that some find the term "deferred consent" problematic given that it incorrectly implies that consent may be sought retroactively for research activities that have already occurred.[15] Therefore, we use the term RWPC throughout this document to describe the general process across the locations of interest.

In other cases, the locations have different names for functionally very similar concepts. For instance, the local regulatory bodies responsible for ethical conduct of research are referred to as "Institutional Review Boards" in the US; "Research Ethics Boards" in Canada; "(EC) Ethics Committees" in the EU; and "Research Ethics Committees" in the UK. We will refer to these organizations as ECs in this document. Another example is the term used to describe the subject's representative from whom informed consent would be sought on behalf of the subject if time allowed. In the US this person is titled the "legally authorized representative"; in Canada, the "authorized third party"; in the EU, the "legally designated representative"; and in the UK, the "legal representative." We will refer to this person as the "AR." Of note, this terminology has caused past confusion, with some member countries of the EU interpreting it requiring a court order to designate the AR's role.[12]

Importantly, the term "subject" or "participant" may refer to an incapacitated adult or a minor experiencing a medical emergency. In each of these locations, minors are allowed to be enrolled in RWPC and are functionally similar to incapacitated adults in terms of meeting RWPC requirements. However, research plans for minors may differ, given that outside of emergency research, it is typical to have an AR (often a parent or guardian) make decisions about research on the child's behalf (with assent if possible), whereas an adult with capacity would make their own decisions. Additionally, children are more likely than adults to have their AR present during a medical emergency. This may affect the feasibility of obtaining consent and/or notification of RWPC after enrollment.

Finally, the concepts of "informed consent" and the "therapeutic window" appear to be consistent across locations, but given their key roles in RWPC, we provide definitions here. Though the specific elements required to be included in informed consent may vary in these locations, the general principles for the purposes of this review refer to the process of "providing a potential subject with adequate information to allow for an informed decision about participation in the clinical investigation, facilitating the potential subject's comprehension of the information, providing adequate opportunity for the potential subject to ask questions and to consider whether to participate, obtaining the potential subject's voluntary agreement to participate, and continuing to provide information as the clinical investigation progresses or as the subject or situation requires ... This process must occur under circumstances that minimize the possibility of coercion or undue influence."[16] This characterization illustrates the fact that informed consent is an extensive and time-intensive process that cannot feasibly or ethically be accomplished during medical emergencies.

As quoted from the US Food and Drug Administration (FDA) guidance document on RWPC, the therapeutic window is "the time period after onset of the event, based on available scientific evidence, within which the investigational product must be used or administered to have its potential clinical effect."[17] This also represents the period in which the prospective subject's AR must be contacted, if feasible. Given the time-sensitive nature of cardiac arrest, the therapeutic window for intra-arrest interventional trials may be non-existent. Conversely, in trials examining post-arrest care interventions, the therapeutic window may be a few hours or more, making informed consent by an AR feasible for some patients. In order for RWPC to be permitted in this circumstance, investigators must show that limiting the study only to patients whose AR was able to give valid informed consent would significantly bias the results and/or unduly delay completion of the study.[17] In these trials, investigators must commit to obtaining consent for the cases in which it is feasible.

Qualifying criteria for RWPC

The basic principle underpinning RWPC is the fact that prospective informed consent cannot be obtained for the individual experiencing

the medical emergency, yet rigorous interventional trials are necessary to improve outcomes for these patients. In light of this dilemma, the Declaration of Helsinki, a cornerstone of ethical human subjects research, recognizes this as a circumstance in which an exception to prospective informed consent is acceptable:

> "Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative."[3]

As prospective informed consent is the gold standard in preserving individual autonomy, a high bar must be set for use of alternative consent models such as RWPC. Therefore, the onus is upon the researchers to provide compelling justification that a departure from the norm of prospective informed consent is required for the study to be conducted. Consequently, each set of regulations stipulates the conditions under which RWPC for emergency medical conditions is permitted. The criteria most consistent across locations are that: (1) the study pertains to an emergency medical situation; (2) the prospective subject is unable to consent; and (3) the prospective subject's AR is unable to provide consent within the therapeutic window (Table 1).

Nevertheless, subtle differences exist between the regulations, some of which may impact the types of research allowable in each location. For example, the US regulations specify that the research must pertain to a "life-threatening" emergency, while the remaining locations are less specific about the types ~~e~~mergencies that can be studied under RWPC (Table 1). Considering most medical emergencies can be viewed as life-threatening, the scope of this discrepancy is narrow and does not apply to cardiac arrest research. However, investigations involving emergency interventions for threatened limbs, sight or other non-fatal loss of function may not be allowable under the US legal framework. Another discrepancy between these locations is the description of the acceptable balance of potential risks and benefits for RWPC. Here, the EU regulations appear the most stringent in their threshold for risk, stipulating that the risk imposed by trial participation must be minimal in comparison to standard care.[4] Conversely, the US, Canada and the UK allow a balance of potential risk with potential direct benefit to the participants However, the impact of this discrepancy is less clear as "minimal risk" may be interpreted differently in each location and/or by the local EC.

A summary of qualifying criteria for RWPC by location is presented in Table 1, including direct supportive quotations from each set of regulations. Table 2 lists key study procedures for RWPC and whether they are required in each location, discussed in detail below.

Activities prior to study commencement

One unique aspect of the US regulations is the requirement for certain activities to be performed prior to the commencement of RWPC, including Community Consultation and Public Disclosure (described below).[6] As part of the trial protocol, investigators must outline their plans for these activities which then must be approved by both the local EC and the FDA sequentially before they are carried out. Upon completion, the results of the Community Consultation must be reviewed, and based on the community feedback, changes to the protocol may be required before the study is approved. As these activities are community-specific, multi-center trials must complete these activities at each site. While Community Consultation and Public Disclosure are aimed at providing additional protections for vulnerable patient population, these activities are often time-consuming, expensive and may require outside expertise, thus adding significant burden to investigators.[18–20] However, it remains unclear how effectively these activities achieve the overarching goal of protecting individuals who are enrolled in these studies.

In the RWPC guidance document published by the US FDA, community consultation is defined as "the opportunity for discussions with, and soliciting opinions from, the community . . . from which the study subjects will be drawn."[17] While specific standards to fulfill these requirements are not outlined, suggested activities include community meetings, focus groups and surveys. The FDA document further describes the goals of Community Consultation, which predominantly identify these activities as a means of showing respect for the community.[17] While community involvement in trial design may be appropriate for many studies regardless of RWPC, the potential benefit for an individual subject who did not participate in these activities is unknown, as even consultation with a large number of individuals in a community does not guarantee that an enrolled individual would hold similar opinions or values. This uncertainty is especially true considering the commonly-cited criticisms that key elements of Community Consultation remain undefined, including the composition of the community to be consulted and a standard level of community acceptance that must be met in order to proceed with the trial.[18]

Public Disclosure prior to study initiation is defined as the "dissemination of information about the emergency research sufficient to allow a reasonable assumption that the communities are aware of the plans for the investigation, its risks and expected benefits, and the fact that the study will be conducted without obtaining [prospective] informed consent for most or even all subjects."[17] Suggested activities include distribution of study information via websites, public announcements/advertisements and presentations, among others. While in theory, the goal of making communities aware of ongoing RWPC seems appropriate, in practice, these activities typically only reach a very small proportion of the target population at risk for the medical condition of interest. As the likelihood of an individual having knowledge of the study prior to enrollment in RWPC is exceedingly low in most cases,[21] the particular subject's autonomy is likely no more protected than it would be without Public Disclosure.

While Canada, the EU and the UK do not require such activities, Canada's regulations do state that the "prospective participants for emergency research are owed special ethical obligations and protection commensurate with the risks involved. Their welfare should be protected by additional safeguards, where feasible and appropriate."

Table 1 – Qualifying criteria for performing RWPC by location.

Qualifying Criterion	US	Canada	EU	UK
Type of emergency	"A life-threatening situation that necessitates urgent intervention"	"A serious threat to the prospective participant requires immediate intervention"	"A sudden life-threatening or other sudden serious medical condition"	"If treatment is being, or is about to be, provided . . . as a matter of urgency"
Existing Treatments	"Available treatments are unproven or unsatisfactory"	"Either no standard efficacious care exists, or the research offers a realistic possibility of direct benefit to the participant in comparison with standard care"	Not explicitly stated	Not explicitly stated
Necessity to Perform Research During a Medical Emergency	"Human subjects are in a life-threatening situation . . . and collection of valid scientific evidence is necessary to determine the safety and effectiveness of the intervention"	"Certain types of medical emergency practices can be evaluated only when they occur, hence the need for this exception"	"The clinical trial is of such a nature that it may be conducted exclusively in emergency situations"	"Having regard to the nature of the clinical trial and of the particular circumstances of the case it is also necessary to take action for the purposes of the clinical trial as a matter of urgency"
Subject's Ability to Consent	"The subjects will not be able to give their informed consent as a result of their medical condition"	"The prospective participant is unconscious or lacks capacity to understand the risks, methods and purposes of the research project"	"Due to the urgency of the situation . . . the subject is unable to provide prior informed consent and to receive prior information on the clinical trial"	"For a subject who is a minor or an incapacitated adult" (implicit)
Third Party Consent	"The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible"	"Third party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so" AND "The delay to seek authorized third party consent could seriously compromise that individual's health"	"It is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative"	"It is not reasonably practicable to [obtain informed consent from the subject's legal representative]"
Prospective Identification of Subjects	"There is no reasonable way to identify prospectively individuals likely to become eligible for participation "	Not explicitly stated criterion, but "procedures to identify prospective participants in advance so that consent may be sought prior to the occurrence of the emergency situation" are suggested as an additional safeguard where feasible and appropriate.	Not explicitly stated	Not explicitly stated

Table 1 (continued)

Qualifying Criterion	US	Canada	EU	UK
Balance of Risks and Benefits	"Participation in the research holds out the prospect of direct benefit to the subjects" AND "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"	"Either no standard efficacious care exists, or the research offers a realistic possibility of direct benefit to the participant in comparison with standard care" AND "Either the risk is not greater than that involved in standard efficacious care, or it is clearly justified by the prospect for direct benefits to the participant"	"There are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition" AND "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"	For minors: "Some direct benefit for the group of patients involved in the clinical trial is to be obtained from that trial." OR For incapacitated adults: "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" AND "The clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and the minor's stage of development [or] the cognitive abilities of the [incapacitated adult] patient" AND "The risk threshold and the degree of distress have to be specially defined and constantly monitored"
Practicability of Investigation Without the Exception of Prior Consent	"The clinical investigation could not practicably be carried out without the waiver"	"It is impossible or impracticable to carry out the research and to address the research question properly, given the research design, if the prior consent of participants is required"	Not explicitly stated	Not explicitly stated

(*continued on next page*)

Table 1 (continued)

Qualifying Criterion	US	Canada	EU	UK
Subject's Prior Objections	*Not a stated criterion, but opt out procedures may be instated (though not required)	"No relevant prior directive by the participant is known to exist"	"The investigator certifies that he or she is not aware of any objections to participate in the clinical trial previously expressed by the subject"	"[If an adult] prior to the onset of incapacity, refused to give informed consent to taking part in the clinical trial, that person cannot be included as a subject in the clinical trial"
EC Approval	Not specified in RWPC legislation but required in general clinical trials legislation	Not specified in RWPC legislation but required in general clinical trials legislation	Not specified in RWPC legislation but required in general clinical trials legislation	"[The trial] is carried out in accordance with a procedure approved by an ethics committee or by an appeal panel . . . at the time it gave its favourable opinion"

RWPC, Research without prior consent; EC, Ethics Committee;
This table refers only to the national/supranational regulations for each location. The states, territories, provinces or member countries within each country/union may have additional laws on the subject which are not reflected in this table.

One of the suggested activities in this section includes consideration of "consultation with former and prospective participants," which may consist of activities similar to the US Community Consultation. Experts in pediatric RWPC in the UK have suggested similar approaches to community interactions, but are not included in the regulations as a formal requirement.[22]

Enrollment procedures

While regulations in each location align on the conditions of the inability to obtain valid informed consent from either the prospective subject or their AR within the therapeutic window, the US regulations require additional steps to be taken before the subject may be enrolled. Specifically, investigators must commit to providing the "opportunity to object" to the subject's study participation within the therapeutic window, "if feasible." This opportunity is not only extended to the AR, but even to an alternative non-AR family member if the AR is unreachable. While the opportunity to object may only be a very brief discussion about research participation, the requirement ostensibly augments the potential for patient/family autonomy while acknowledging the inability to meet all the elements essential to informed consent during the emergency.

Though the opportunity to object attempts to offer additional protections to vulnerable patients, its implementation may not be effective in many cardiac arrest trials involving RWPC and represents an additional barrier to study enrollment. Given the unpredictable and urgent nature of intra-arrest interventions, it is often the clinical team, not a research team member, who is responsible for enrollment and administration of the investigational intervention. Therefore, providing the opportunity to object may require additional training for a large group of clinicians and/or providers. Furthermore, cardiac arrest is one of the most extreme and time-sensitive medical emergencies, and providing an opportunity to object may be predictably infeasible. Even if the AR is present, attempts at discussing research within the therapeutic window may have untoward consequences, including distraction or cognitive overload of the clinicians managing the event; additional stress on the AR during their loved one's crisis; or even the AR's distrust about the clinicians' priorities.

A more minor differentiation between regulations is the explicit requirement for the study team to document all attempts to contact the subject's AR, either for consent (US and Canada) or the opportunity to object (US). This documentation does not appear to be obligatory in the EU or the UK.

Post-enrollment procedures

Notification of enrollment either to the AR and/or the subject as soon as feasible is required in all four sets of regulations, but the discussion after notification may differ based on how consent in RWPC is viewed in each location. In the US, once the patient is enrolled in RWPC, they do not need to provide written informed consent if they wish to continue participation. However, in Canada, the EU and the UK, informed consent must be sought for continued participation from the subject or the AR as soon as feasible. Some experts in the UK have also interpreted the RWPC laws to require consent for use of the data that was collected prior to obtaining consent,[23] but the legislation lacks detail on the topic.

Table 2 – Required RWPC study procedures according to national or supranational legislation by location.

Procedure	US	Canada	EU	UK
			Required?	
Prior to Study Commencement				
Community Consultation	Yes	No. May be considered as an added protection for a vulnerable population.	No	No
Public Disclosure	Yes	No	No	No
At Time of Enrollment				
Provide the Opportunity to Object to Participation to an AR* During the Therapeutic Window	Yes, if feasible.	No	No	No
Documentation of Attempts to Contact an AR*	Yes	Yes	No	No
Post-Enrollment				
Notification of Enrollment to an AR* and/or Subject if He/She Regains Capacity	Yes	Yes	Yes	Yes
Notification of Enrollment to an AR* if the Subject Dies Prior to Notification	Yes, if feasible.	Yes, if "possible, practicable and appropriate"	No	No
Consent for Ongoing Participation After Enrollment	No	Yes	Yes	Yes
Consent for Use of Data Collected Prior to Notification if the Subject Dies Prior to AR* Notification	No	No	No	No
Subject or AR Offered to Withdraw Previously Collected Data if Consent is Declined	No	Yes, if "possible, practicable and appropriate"	Yes	No
Following Study Completion				
Public Disclosure	Yes	No	No	No
Other Regulatory Requirements				
Study-Specific Government Oversight	Yes. FDA oversight required for all RWPC (IND/IDE)	Not specified in RWPC legislation but Health Canada oversight generally required for clinical trials	Not specified in RWPC legislation but EMA and member country agencies oversight generally required for clinical trials	Not specified in RWPC legislation but MHRA oversight generally required for clinical trials
Enhanced Electronic Records	Yes. Part 11 of Title 21 of the Code of Federal Regulations applies to all RWPC (IND/IDE)	No	No	No
Independent Data Monitoring Committee	Yes. Required for all RWPC and also standard practice for most clinical trials	Not specified in RWPC legislation but standard practice for most clinical trials	Not specified in RWPC legislation but standard practice for most clinical trials	Not specified in RWPC legislation but standard practice for most clinical trials

RWPC, research without prior consent; AR, authorized representative; FDA, Food and Drug Administration; IND, Investigational New Drug; IDE, Investigational Device Exemption; EMA, European Medicines Agency; MHRA, Medicines and Healthcare Products Regulatory Agency.

This table refers only to what is stated in the national/supranational regulations for each location and does not necessarily reflect common practice or requirements commonly enforced by ECs. Additionally, the states, territories, provinces or member countries within each country/union may have additional laws on the subject which are not reflected in this table.

* In the US, a non-AR family member must be offered the opportunity to object and/or notified of enrollment if the AR is unreachable.

While subjects and their ARs across all locations retain the right to withdraw from further participation at any time, in the EU they also must be notified of their right to withdrawal previously collected data if they chose to decline consent. In Canada, participants or their AR must be provided the option to request withdraw of their data and/or biological materials "unless this option is impossible, impracticable or inappropriate." For example, data removal may be considered inappropriate if it threatens the scientific validity of the study as this would have direct bearing on the respect for contributions of other participants. In the US, the investigator may continue to use previously collected data, even if the subject discontinues participation upon notification. According to the FDA guidance document, this is due to the risk of potential bias from subjects withdrawing these data which may compromise the integrity of the study, making safety and efficacy data difficult to interpret.[17] In the UK, management of previously collected data is not specifically discussed in the regulations and may therefore be determined by the EC on a case by case basis.

Another challenging scenario in post-enrollment discussions arises when the subject dies before the study team is able to contact his or her AR. In the US regulations, the investigator is required to notify the AR or other family member about the deceased subject's trial participation, if feasible.[6] This may include phone or mail notification several weeks after the subject's death. Regulations in Canada, the EU and the UK do not specify the actions required in this scenario, and therefore, the investigator must justify their plans for these cases to the EC for approval. It also appears that there may be some room for interpretation on the topic. As mentioned above, in Canada, notification of enrollment in RWPC and seeking informed consent are required "if possible, practicable and appropriate." Therefore, an investigator could make the argument to the EC that a subject's death prior to deferred consent constitutes an exception to these requirements. In the EU, the Dutch Central Committee on Research Involving Human Subjects argues that once the subject has died, there is no longer a formal legal role for the AR, and therefore that person may not provide deferred consent. As long as consent cannot be sought, data may continue to be used. Still, they support that the AR should be notified of the subject's enrollment and propose that it is reasonable to honor an AR's or family member's wishes to exclude the subject's data depending on the circumstances.[24] In contrast, some experts in the UK endorse the need to obtain consent for data use in the case of bereaved families as they would for non-bereaved families,[23] though this concept is not universal.[25] In fact, investigators have obtained EC approval to not directly notify relatives of their involvement in RWPC for subjects who died early in an out-of-hospital cardiac arrest trial.[26] In this case the burden on the bereaved relatives of being directly contacted regarding research consent was felt to outweigh the potential benefits.

Activities following study completion

Following the completion of the study, the US regulations require a second Public Disclosure, aimed at publicizing the results of the research to ensure that communities and researchers can learn from the work, regardless of the findings. In addition to scientific publication and reporting on clinicaltrials.gov, the investigator must also disclose the results to the community in which the research takes place. Again, there are no specific guidelines on how this must be accomplished, and it is up to the EC and FDA to approve plans for Public Disclosure after trial completion. Such activities may be as simple as sharing the published work on a website or targeted social media groups. Canadian, EU and UK regulations do not include these specifications. Since Public Disclosure after study completion can be simple and cost-effective and requires little additional effort, the burden on the investigational team is often low.

Other regulatory requirements

In addition to EC approval, interventional drug trials (regardless of RWPC) in Canada, the EU and the UK typically require government regulatory oversight (e.g. Health Canada, European Medical Agency, Medicines and Healthcare Products Regulatory Agency). In contrast, most trials involving drugs already on the market in the US do not require FDA oversight.[27] However, the US regulations stipulate that all RWPC must be performed under an Investigational New Drug (IND) or Investigational Device Exemption (IDE) with the FDA.[6] This obligation has several downstream effects representing significant barriers for US investigators to which they would not otherwise be subject. For example, having a second regulatory body in addition to the EC results in a staggered approval process for both (1) the initial review of the protocol and Community Consultation and Public Disclosure plans; and (2) the subsequent review of the results of the Community Consultation and final approval to proceed with the trial (as detailed above). Because any changes to the protocol requested by one agency at any stage in the process must subsequently be approved by the other, this structure may significantly delay study approval. Additionally, studies performed under an IND/IDE in the US must comply with Part 11 of Title 21 of the Code of Federal Regulations in regards to electronic study records.[28] These regulations specify procedures not only to ensure the confidentiality of electronic records, but also the authenticity and integrity of the data. These tools require rigorous system validation, authority checks and time-stamped audit trails (among other requirements), which are not available in many commonly used electronic data collection software programs. Therefore, investigators may need to purchase specific data collection programs that they are unfamiliar with, leading to additional cost and time invested into the research team training on a new system. Given that government regulatory oversight is standard for most clinical trials in the other countries/unions, RWPC does not appear to add any incremental burden in this regard.

Finally, of the countries/unions reviewed here, the US is the only one which specifies that RWPC studies must use an independent data monitoring committee.[6] However, given this is standard practice for most interventional trials in the US, this requirement does not add significant burden to the study team. Although not explicitly stated in the other RWPC regulations, use of a data monitoring committee for interventional trials is also standard in the remaining locations.

Limitations

This narrative review reflects the perspectives of investigators in resuscitation science. Our expertise lies in real-world application of these regulations rather than legal theory or practice. Furthermore, this review focuses on regulations specific to RWPC, and does not represent an exhaustive review of all clinical trials regulations for

each location. Finally, we recognize that the locations reviewed here are limited to Western countries and cultures whose views of consent and RWPC may differ from other parts of the world.

Conclusion

Regulations governing RWPC in the US, Canada, the EU and the UK focus on similar goals and protections for vulnerable populations during medical emergencies. Differences in the qualifications for invoking these rules and their implementation exist across the locations which may affect study design. US regulations present added barriers to performing RWPC which are not present in Canadian, EU or UK requirements. It remains unclear whether these additional barriers add significant protections for individuals enrolled in RWPC compared to other Western locations with similar legislation.

CRediT authorship contribution statement

Catherine E. Ross: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Melissa J. Parker:** Writing – review & editing, Investigation, Data curation. **Spyros D. Mentzelopoulos:** Writing – review & editing, Investigation, Data curation. **Barnaby R. Scholefield:** Writing – review & editing, Investigation, Data curation. **Robert A. Berg:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

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