

Research ethics committees in laboratory medicine

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ABSTRACT

Biomedical research that involves human subjects requires compliance with ethical principles and guidelines. The ethical and scientific standards of research have been thoroughly discussed by international ethical guidelines and declarations. Compliance with these ensures the autonomy, dignity and well-being of research subjects; as well as the integrity and credibility of research results. Research ethics committees (RECs) are mandated to ensure that research proposals are scientifically sound and ethical. In this review, we define RECs in laboratory medicine and describe their role based on the examination of the requirements of ethical research; discuss particular ethical issues that arise in laboratory medicine research using biological samples, what challenges they face and how they can ensure the quality of their review. RECs need to be put into a broader framework that ensures institutional governance with continuous evaluation and auditing that ensure the quality of ethical review.

INTRODUCTION

There has been a global increase in research productivity during the last decades. A potential concern with that is the adherence of these researches with ethical principles and the safeguarding of research participants. A balance between human subject protection and the progress of science should always be maintained.

Laboratory medicine like any other medical disciplines is bound to adhere to ethical standards in practice and research. Yet, there is still great variability in research ethics education in laboratory medicine programs (1). With advancements in the field and complexities arising in research, biomedical researchers and research ethics committees should be well trained to identify unique ethical issues that arise during the process of ethical review. Some of these ethical issues represent some new dimensions to old themes. Some of these include the use of biological samples that remain following routine investigation, sometimes using additional research tests in surplus of clinical requirements, storage of samples, research commercialization, methodology validation or methods comparison as well as incidental findings in genetic research, etc. A large proportion of the research in the field is retrospective where the conventional human subject is not directly involved. This poses an important question whether this type of research requires ethical approval and informed consent (2).

In this review, the role of research ethics committees (RECs) in ethical review, their operational function, particular issues arising for RECs in laboratory medicine along with their challenges and opportunities will be comprehensively discussed.

RECs or their equivalent, the institutional review boards (IRBs), are committees that provide protection to research subjects through their mandate of providing independent ethical and

scientific review of research proposals (3). They play a pivotal role in enhancing the quality of research conducted within educational and clinical institutions. They are also considered as a bridge between researchers, institutions, and ethical guidelines.

The primary mandate of RECs is to review research proposals before any data collection ensues. This process includes a rigorous scientific review and a detailed examination of ethical issues that may arise. This ensures research subjects are respected, autonomous and not exposed to excessive risks without direct benefits. Additionally, RECs have a secondary mandate of protecting the integrity of their research institution from any misconduct that may tarnish their reputation and result in public mistrust (4).

THE ETHICAL FRAMEWORK FOR RESEARCH EVALUATION BY RECs

In 2000, Emanuel *et al* published a systematic framework consisting of seven general requirements that make human subject research ethical (5). This practical framework is a valuable tool to guide the review process conducted by RECs. We use this framework in relevance to laboratory medicine to discuss particular ethical issues. These requirements should be satisfied by research proposals before a REC grants final approval.

1. Social value

The submitted research and expected findings should lead to advancement in laboratory medicine knowledge.

2. Scientific validity

The research should be methodologically sound with clear scientific aims and objectives. It should not be biased, minimize confounders, and use the right analytical tests. Ethical research should be conducted in a rigorously sound methodological

approach. As stated in the CIOMS guidelines: “Scientifically unsound research on human subjects is *ipso facto* unethical in that it may expose subjects to risks or inconvenience to no purpose.”

The research methodology and data analysis must be valid, sound, and feasible. The methods used and sampling must be appropriate to achieve the research objectives. A research that is scientifically invalid will not enable the achievement of the overall research goal and therefore will expose subjects to unnecessary risks (6). Methodological scrutiny in laboratory medicine is of great importance. Different methodologies may exist to perform a single test; all of which differ in their sensitivity, specificity, positive and negative predictive values. Some tests may be quantitative, semi-quantitative while others are qualitative. Issues that arise in the pre-analytical, analytical and post-analytical phases should also be taken into consideration. It is therefore important to have the right expertise to scrutinize laboratory methods among REC membership.

3. Fair subject selection

The selection of enrolled subjects should be fair to ensure the principle of distributive justice is achieved (7)(8). It should ensure that no vulnerable populations are chosen without a justification. It should also ensure that inclusion and exclusion criteria are clear. Fair subject selection implies that, as much as possible, individuals who will bear the burdens and harms of the research should be able to enjoy its benefits and those who will benefit from research should share some of the anticipated risks. Retrospective research on biological samples is often anonymous or anonymized and therefore no issues arise from subject selection since the identity of samples cannot be readily ascertained. In a prospective study, the selection of a vulnerable population (e.g children) is not justified if the research can equally be conducted in adults.

4. Favorable risk-benefit ratio

Favorable risk-benefit ratio should ensure that there is an acceptable risk-benefit ratio and embodies the moral principles of beneficence and non-maleficence (7)(8). Beneficence implies that the benefits of research should be maximized as much as possible. In laboratory medicine, few increments above minimal risk are identified particularly in genetic research(9). Although researchers aim to ensure confidentiality of research subjects at all times, it is difficult in the era of genomic datasets and electronic health records to be certainly sure of that. Non-maleficence implies that harm should not be disproportionate to the benefits.

5. Informed consent

Informed consent is the application of the moral principle of respect for persons and autonomy (7)(8). It allows individuals to control their decisions and ensures that they make independent, informed decisions whether they want to be part of a research or not. To give informed consent, individuals must be informed about: the purpose of the research, its description, the anticipated risks, the potential benefits, the confidentiality of participants, any compensation for injury if applicable, and a reference person from the research team who should address any questions. It should be emphasized that participation is voluntary and withdrawal is possible without any negative consequences. The decision-making should be free of coercion, undue influence, or pressure. Participants should be competent and have adequate understanding of the information. Surrogate or proxy consent should be obtained in the case of incompetent individuals. Research in laboratory medicine does not always need informed consent; this is the case in anonymous and anonymized biological samples. In general, coded and prospective samples require informed consent since the risks of privacy and confidentiality are present.

6. Independent review

In laboratory medicine, research stakeholders have different interests which may differ from those of the participants and thus conflict of interests (COI) may arise. There are often collaborations between industry and academia. Some REC members may also have COI such as being consultants or own shares in biomedical companies. Maintaining the independence of RECs review is vital to research governance and public accountability. This is usually achieved by having clear COI policies. CIOMS require that RECs members should not review research in which they have competing direct interests as investigators or funders (6). Including a lay person or a public representative as a REC member contributes to the independence of review.

7. Respect for human subjects

Research subjects should be respected throughout the research process. Their privacy and confidentiality should always be maintained. Any new information that arises should be made available and disclosed to the participants. Permitting subjects to withdraw and change their mind during the research is key to achieving autonomy and ensuring the welfare of subjects is always respected.

RECs: STRUCTURE, ETHICAL ISSUES AND CHALLENGES

RECs were originally established to protect the health, safety and wellbeing of researchers and of research participants. Over time, their role has been expanded and diversified beyond the ethical review to rather become a role of research governance. Previous comments have described them as “gatekeepers or “adjudicators” (4). Whittaker suggests that: “ethical review boards have become established as one of the most authoritative, if not authoritarian, gatekeepers in research history” (10). For these

reasons, it is important to ensure RECs have the right membership.

Different institutions have different membership for their ethical committees. Albeit, there is a consensus that the membership is generally multidisciplinary with broad representation from across specialties.

Additionally, a member of the community that represents its values and norms in the committee, contribute to the independent review and RECs’ efforts to maintain transparency and accountability to the public (11). He/she may also reflect the public’s nonscientific point of view and opinions; and ensures that the informed consent is comprehensible to the nonscientist research person.

There is no specific guidance on the membership of RECs in laboratory medicine but it is agreed that whenever expert advice is needed for complex proposals then the appropriate consultants (eg. Clinical chemist, immunologist, geneticist, hematologist, etc) may be called upon by the REC (Table 1).

ETHICAL ISSUES IN RESEARCH USING BIOLOGICAL SAMPLES

Blood samples and the human subject

RECs evaluating proposals in laboratory medicine often encounter complex ethical issues that differ from their clinical counterpart mainly due to the nature of research that uses blood samples and human tissues (figure 1). These samples and data are not the living, identifiable humans that research regulations were designed to protect. Many ethical debates discussed whether research on blood samples is human subject research. Federal regulations define a human subject as a “living individual about whom an individual conducting research obtains data through intervention or interaction with that individual or identifiable private information” (14). Albeit,

Table 1 Regulatory requirement of RECs

Regulation	Requirement
Membership	<ul style="list-style-type: none"> • At least 5 members of varying backgrounds with equal gender opportunities • At least 1 scientific member, 1 nonscientific member, and 1 unaffiliated member • The chair should not be a member of the institution • Members should have adequate experience and expertise to safeguard subjects' rights and welfare. Expertise should include research methodology, ethics and laws, regulations, institutional commitments, and professional standards; as well as content expertise in the different fields of biomedical research. Avoid selection bias • At least 1 member knowledgeable about research in vulnerable groups • Members should declare conflicts of interest • Ad hoc experts or independent consultants invited as needed
Function	<ul style="list-style-type: none"> • Quorum requirement (more than half members); with distribution of expertise requirements over the quorum • a confidentiality agreement regarding meetings, applications, information on research participants, and related issues should be signed by members;
Review	<ul style="list-style-type: none"> • Meetings should be planned in advance according to the workload allowing time to study submitted documents beforehand • Approve, ask for corrections and disapprove research • Follow a systematic scientific and ethical framework for review • Approve informed consent and ensure suitability • Waive the requirement for informed consent whereas applicable
Documentation & archiving	<ul style="list-style-type: none"> • All meeting minutes of RECs • Submitted protocols, corrections, approval and disapproval decisions • Correspondence between REC members; and applicants • Follow up • Final reports of studies

The table summarizes the operational guidelines of RECs including the membership terms, function, review, documentation and archiving in accordance to the World Health Organization guidelines and the Common Federal Rule (12) (13) (14).

a lot of biomedical research is carried out on deceased people or on biological materials donated before death. Although these are not living subjects but the protection of the interests of the deceased is increasingly recognized as respect for persons ethical principle (7)(15).

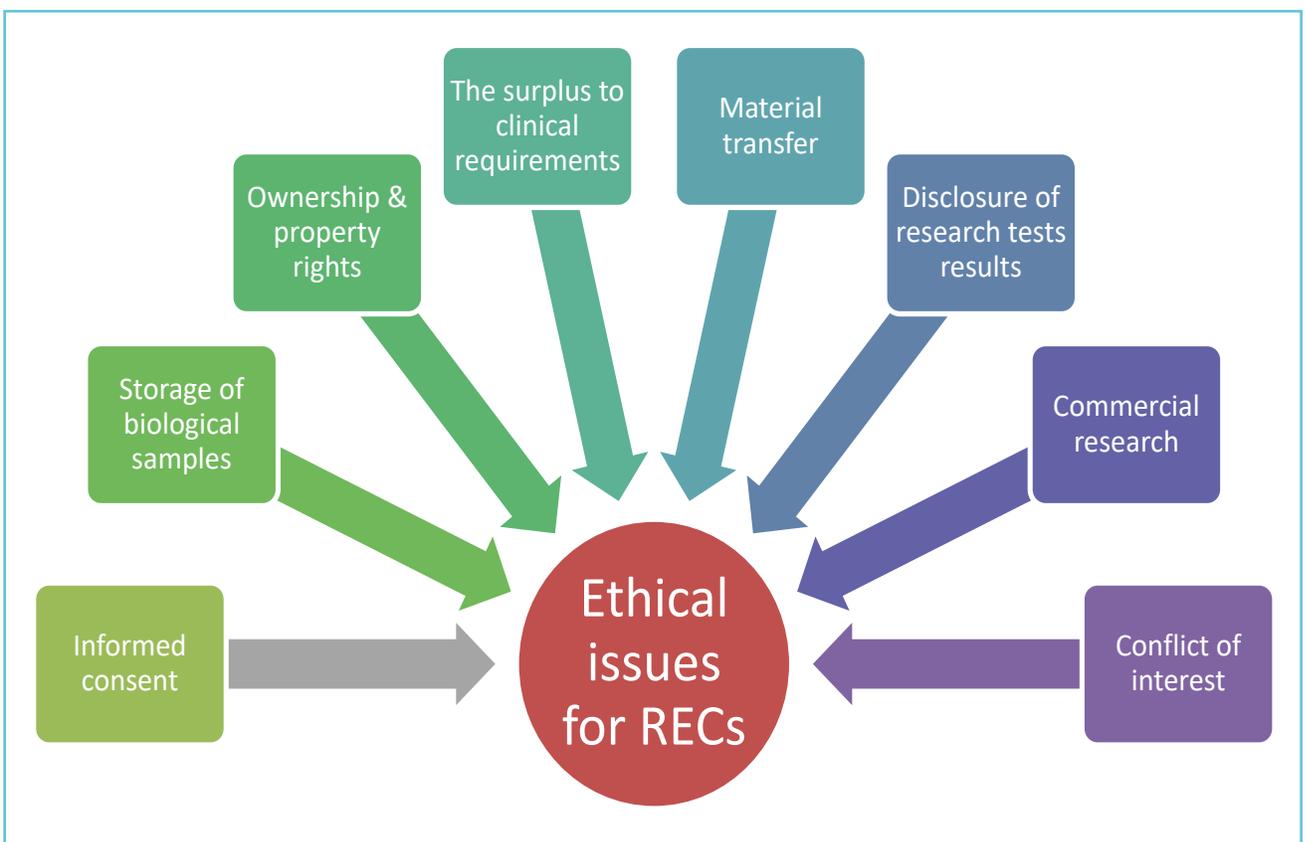
Informed consent

Research in laboratory medicine commonly involves existing samples in which the participants did not give consent to, but such research may be quite valuable. What counts as informed consent when a sample may be stored for years and used for unforeseen research? The traditional concept of informed consent where a participant is informed about the important aspects of a study (purpose, risks and benefits) may not

be a good fit for research with bodily materials and data stored for future purposes. In many instances, a broad consent has been suggested to overcome such hurdles. Yet, it is still argued that a broad consent is not bona fide consent and thus, the concept of autonomy is not really fulfilled. Obtaining consent under institutional status quo may not necessarily be a consent that ensures autonomy of research subjects but is rather safe for regulatory purposes.

RECs should thoroughly discuss what would be the best model of informed consent to be used in such cases. Issues to be discussed within the informed consent include the storage of samples for future research and whether samples may be part of a repository or a biobank (Figure 1).

Figure 1 The ethical issues encountered by research ethics committees in laboratory medicine



Material transportation, ownership and commercialization.

Research in laboratory medicine may sometimes require the transfer of biological sample to different institutions or even countries in international collaborations. Material transfer agreement is a process to facilitate exchange of samples and technology between researchers and institutions and to protect the interest of both (16). It is usually an agreement on materials that are owned by the originator but of which has no propriety rights or patents (17) (18). Although this can be a simple process, more complexities are gained with the increment in collaborations between industries and academia. There has also been an increasing movement in universities to commercialize their research (18). Biotechnology research has also been changing and moving towards genomics and generation of *in vitro* research models, nucleic acid tools, molecular probes for drug discovery and other tools that are meant to be disseminated (19).

Many disputes have arisen over the ownership of leftover “abandoned” blood samples. There are no specific regulations to govern this issue. However, the interest of research participants should always be safeguarded. Many bioethicists

consider subjects to no longer have any property or ownership rights over the material (20). This is because leftover materials are no longer functional. Some participants have expressed even if the donor has no continuing property right, the laboratory must act in accordance with ethical regulations if this material is to be used for research (21). It is for RECs to ensure that the confidentiality of the data is kept by researchers all time.

Commercialization of research and commercial spin-off companies may automatically imply a COI for RECs which may not always be the case in research. For instance, a researcher who is developing a diagnostic method may not acquire enough funding to develop such tool. However, biotechnology companies may be interested to sponsor such type of research. This collaborative partnership could result in a synergistic relationship that may lead to the development of new knowledge. It is therefore important for RECs to understand such complex entities and ensure that benefits are not skewed towards companies nor researchers are driven by competing interests (Table 2).

Table 2 General guidelines for researchers in laboratory medicine before conducting research on human tissue specimens

1.	Understand the regulations in reference to biological samples and laboratory medicine.
2.	Understand the components of informed consent form in biological samples research (specially in genetics).
3.	Inform research participants as much as possible about risks, how their specimens will be used now and in the future, plans to return incidental findings.
4.	Have research protocols and informed consent forms reviewed and approved by a REC.
5.	Always maintain confidentiality.
6.	Understand when a waiver of informed consent can be obtained by REC.

CHALLENGES

RECs have been criticized generally for a number of issues. The administrative work of RECs has been previously described as a slow bureaucratic process (22)(20) (23). It is also costly and serves little to enhance the quality of the research process (24) (25). There have been suggestions to reassess RECs to ensure their purpose is fulfilled to encourage research within acceptable ethical frameworks. However, there are still no metric tools that could assess and measure the effectiveness of RECs (26) (13).

Sometimes, inflexible requirements for adherence to narrow literal interpretations of regulations and other policies have led to a system that is more concerned with “legal” protection of the institution than the protection of human research participants (18) (27). Some challenges that face RECs are the inconsistencies across different committees even though they may be using the same guidelines (28). However, Edwards *et al* argue that not all inconsistencies should be perceived negatively and may sometimes be considered a desirable part of research (29). This possibly has its origin from a moral pluralism philosophy. However, it is the inconsistencies that are due to the lack of expertise in identifying ethical issues that is undesirable.

In addition to scientific and ethical review, it is crucial for RECs to ensure researchers have sufficient research experience and qualifications or alternatively collaborating with an experienced colleague in the relevant field of research. In the case of laboratory medicine, the researcher needs to provide evidence to the committee that they commit to good laboratory practice, they are trained in laboratory health and safety rules, and they are experienced in using laboratory equipment and techniques. Researchers should ensure they are using the right laboratory method in line with their research objectives. Working with biohazardous materials, with toxic

chemicals or with radioisotopes is risky and must be governed by the bioethical principle of non-maleficence (7) (8), the REC have a duty to minimize the risk of individuals being exposed to harm. Qualifications that ensure the investigators have achieved these competencies or received formal training should be confirmed by RECs in laboratory medicine.

OPPORTUNITIES AND THE WAY FORWARD

The identified challenges faced by RECs point towards an opportunity for quality assurance and continuous improvement (13). Independent auditing is key to a quality assessment that can be followed by accreditation (30) (31). For these purposes, few tools have been previously developed and many local guidelines may include guidelines for accreditation of RECs (18).

RECs maybe unexpectedly be faced with the increasing workload. It is imperative for those committees particularly in laboratory medicine to have well trained members that can efficiently review protocols in due time (32). It is increasingly recognized that adequate training of committee members improves the efficiency of RECs (33). This has been recognized by Levine who emphasizes the need to add an educational system for REC staff and members followed by an accreditation system for RECs and certification system for the staff (31). As the face of biomedical research is changing and gaining complexities, RECs members will need to undergo more formal continuous professional training. Enhancing a model of self-assessment, certification of members and accreditation are all strategies that may be used to ensure the professional research review (22).

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