CLINICAL RESEARCH FOR MEDICAL STUDENTS

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Chapter 1

WHY DO CLINICAL RESEARCH?

To advance medical knowledge

Medicine has developed largely due to observation. This began at the anecdotal level: clinicians would make observations at the patient-level and then share it with colleagues so that their own patients could benefit from that knowledge. Modern clinical research has since systematized this practice of observation. Technological developments have accelerated discovery in the basic sciences, from molecular biology to pharmacology, and it is the role of translational and clinical research to adapt and evaluate these findings for usage in human patients. Clinical research is an incredibly opportunity to apply the scientific method to problems in human health to benefit not only your own patients, but also society at large[1].

Clinical research has taken the form of biomedical research, epidemiological studies, behavioral work, and health services research. The public is most likely familiar with the idea of a clinical trial, in which investigational drugs and treatments are evaluated in volunteer subjects. But with advances in information technology, most new research is based on existing data in the form of databases and biological samples obtained from routine clinical care. This "secondary use of data" spares human subjects and repurposes existing resources, minimizing effort, risks to human subjects, and manpower[2]. Per Nass et al. in 2009"

> "Collectively, these forms of health research have led to significant discoveries, the development of new therapies, and a remarkable improvement in health care and public health. Economists have found that

> medical research can have an enormous impact on human health and longevity, and that the resulting increased productivity of the population contributes greatly to the national economy (Hatfield et al., 2001; Murphy and Topel, 1999) in addition to the individual benefits of improved health. If the research enterprise is impeded, or if it is less robust, important societal interests are affected."[3-4]

Much of what we understand about diseases and treatments is actually a product of clinical research efforts. For instance, by combing through patient records and samples from breast biopsies, it was found that survival and relapse rates related to amplification of the HER2/neu oncogene. This then gave way to the development of Herceptin (trastuzumab), an early entry in the growing field of personalized medicine and biologics[2]. Clinical research also determined that routine mammography substantially reduced deaths due to breast cancer, and thus demonstrated the value and financial worth of preventative services[2,5]. ePrescribing, the ability to send prescriptions directly from electronic medical record programs to pharmacies, is also a product of clinical and health services research.

The peer-review process and online publication enable new findings to be communicated rapidly. Clinicians assess the literature and applications like UpToDate for treatment recommendations daily, enabling the fruits of clinical research to reach real patients in real time. It benefits not only current patients, but also generations to come. Medical research also presents an intellectual challenge which can satisfy personal and academic curiosities. Society's ability to combat disease and care for our neighbors depends on clinical research and the next generation of physician-investigators.

To prepare for a career in academic medicine

There is a wide range of career opportunities and profiles available to physicians after receiving their medical degree and completing residency training. Most assume that their professional career will involve patient care, but this route alone takes on many forms:

- **Private practice** is an excellent choice for those who seek flexibility in practice style, as well as independence and work-life balance.

- **Military medicine** is an option for those who wish to serve and support others in the armed forces, particularly in trauma care.

- **Academic medicine**, primarily built on teaching, research, and clinical care, enables clinicians to conduct clinical research while also contributing to the medical education process.

Hybrid careers are also more and more common, with those in private practice also participating in independent and industrial research projects. Some clinicians also elect to not see patients, either as a full-time research scientists or working in industry, either in consultant or development capacities. These choices are usually the product of both personal and professional preferences, where interest in a particular speciality and a desired lifestyle must often be balanced.

Academic medicine is an important realm because it expands existing medical knowledge and practice while also training the next generation of physicians. Despite its weight, it is often the road less traveled. Many voices, from current academic clinicians to economists, have voiced concerns about the future of academic medicine: medical schools are currently facing staff issues, especially in light of retiring baby boomers and the growing number of medical students and schools, and the number of tenure-track faculty positions is declining.[6,7] Several literature reviews and surveys of the workforce have identified several explanations for this shift away from academia:

- Salary differential and financial disadvantage;
- Bureaucratic and administrative duties and concerns;
- Difficulty in securing funding;

- Lack of familiarity with research;
- Lack of mentorship during training years;
- Less awareness of academic posts compared to clinical practice positions;[8-10]

In addition, recent entries in the literature have sought to identify what factors *do* steer trainees towards academia:

- Research and publication during medical school;
- Research and publication during residency training;
- Familiarity with the medical research process;
- Training at a medical school with a large number of full-time faculty publishing annually;
- Identification of a mentor (an academic faculty member) in medical school and/or residency;[11-13]

From the perspective of medical schools, it is thus incredibly important to expose students to academic medicine and clinical research to ensure a steady supply of future academics. As a medical student, it is important to engage in research early in order to overcome commonly-cited barriers. Students can actually learn an impressive amount about academic medicine while in medical school, and this is best guaranteed with the identification of a research mentor. Under their supervision and guidance, students can:

- Participate in research study design;
- Develop and pen manuscripts for publishing in peer-reviewed journals;
- Learn how to identify and apply for research grants;
- Write and submit abstracts and posters for conferences;

- Speak and present original research at professional meetings;
- Understand how to evaluate the literature and participate in the peer-review process;

To explore a speciality of interest

The most exciting and arduous aspect of medical school is the selection of a speciality for residency and training. This process can be daunting due to the sheer number of specialties to explore, their respective subspecialties and practice styles, and differing expectations for residency applications. While this decision is often made during the clinical years, typically years 3 and 4, it is never too early to start. In fact, exploring potential fields in years 1 and 2 may better inform students as to how to spend elective portions of years 3 and 4, particularly in sub-internships and away rotations.

Pursuing research opportunities in a field of interest is a great way to familiarize oneself to the field. Particularly in extended, long-term research projects, students can be exposed to aspects of a chosen field beyond what they may see on rotation in years 3 and 4. While the specialty itself is often the primary concern, students should also consider lifestyle, patient base, and that field's community.

- Literature reviews will familiarize students with:
    - Field-specific high impact journals;
    - Current areas of research interest;
    - Modern controversies in professional and scientific opinion;
    - Influential names and institutions;
    - Where the field is going;
- Students conducting clinical research can:
    - Learn more about the specialty's patient base and its needs when consenting and following

patients for studies;

- Understand the speciality's relationship with other fields and healthcare professionals;
- Appreciate work-life balance and lifestyle by working alongside current practitioners ;

- When presenting at conferences, students can:
  - Meet potential mentors and explore residency/fellowship opportunities;
  - Meet influential figures in the field;
  - Establish relationships for future collaboration;

To apply to residency programs

While research is by no means required for the residency match, it is one of many factors that committees will use to evaluate and rank candidates. It is especially important in the more competitive fields, such as dermatology, orthopedics, and neurosurgery. Research participation demonstrates a personal interest in the field, a serious commitment to its study, and a dedicated work ethic.

Medical student research is indicated and measured by two metrics in the match process:

- Number of Research Experiences
- Number of Abstracts, Presentations, and Publications

Statistics from the most recent match (2016) are available online at https://www.nrmp.org/wp-content/uploads/2016/09/Charting-Outcomes-US-Allopathic-Seniors-2016.pdf. Details are broken down by specialty, with matched US seniors being compared to unmatched US seniors. By specialty, some numbers of interest include:

Mean Number of Research Experiences of U.S. Allopathic Seniors

Specialty	Matched
Anesthesiology	2.7
Child Neurology	3.1
Dermatology	4.7
Diagnostic Radiology	3.1
Emergency Medicine	2.4
Family Medicine	2.0
General Surgery	3.2
Internal Medicine	2.8
Internal Medicine/Pediatrics	2.5
Neurological Surgery	4.8
Neurology	3.1
Obstetrics and Gynecology	3.2
Orthopaedic Surgery	4.0
Otolaryngology	5.1
Pathology	2.8
Pediatrics	2.5
Physical Medicine and Rehabilitation	8.4
Plastic Surgery	4.6

Psychiatry	2.5
Radiation Oncology	5.1
Vascular Surgery	4.2

Mean Number of Abstracts, Presentations, and Publications of U.S.

Allopathic Seniors

Specialty	Matched
Anesthesiology	3.5
Child Neurology	6.8
Dermatology	11.7
Diagnostic Radiology	4.9
Emergency Medicine	3.3
Family Medicine	2.6
General Surgery	4.7
Internal Medicine	4.4
Internal Medicine/Pediatrics	3.5
Neurological Surgery	13.4
Neurology	5.1
Obstetrics and Gynecology	4.2
Orthopaedic Surgery	8.2
Otolaryngology	8.4

Pathology	5.9
Pediatrics	3.4
Physical Medicine and Rehabilitation	3.9
Plastic Surgery	11.9
Psychiatry	3.7
Radiation Oncology	12.7
Vascular Surgery	8.3

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Chapter 2

FINDING RESEARCH OPPORTUNITIES

Students often cite difficulty in finding research opportunities as a primary barrier to participation in research activities. Interestingly, this phenomenon has been observed across a wide range of medical schools, including those with a particular commitment and investment in student research. Even at schools with widely advertised and transparent access to research opportunities, students are often hard-pressed to find a research project that suits their needs and interests. Identifying a suitable project requires a certain degree of self-awareness for students; consider asking yourself the following when looking for research projects:

- What work am I interested in? What do I *not* want to do?
- Do I want to work with data, in a lab or with patients?
- How much time can I commit to a project?
- Am I interested in a summer opportunity away from my school, or a longitudinal project with my home institution?
- Am I confident enough to work relatively independently from my mentor, or do I work better with more supervision?

Listed below are suggested methods for finding research opportunities, both at your home institution and for extramural opportunities, particularly during M1 summer. Venues for identifying research and actual research opportunities themselves vary incredibly from school to school, so a familiarity with your school's resources is always the first step. We will then conclude with mentor selection: just because you are interested in a specific field or subject does not

mean the newly-found opportunity is the right one for you.

Finding Research Opportunities at Your Home Institution

Lecturers

Most lecturers during the preclinical years are academic faculty, meaning they are interested in scholarly activity. While this often may mean clinical teaching, it more often than not also denotes a personal interest in advancing medicine. If you find a particular lecturer or lecture interesting, speak with them after the lecture or by email (most lecturers provide their contact information during their lecture). Even if they are not currently open to research with medicals students, they may be able to connect you with someone with a similar research interest.

Medical Education Faculty

Your school's administration will keep track of research programs available to students as well as individual students' research activities. Based on your own interests and previous, they may be able to point you towards a specific department or mentor that is particularly amenable to working with medical students. They may also be able to indicate particular programs and funding opportunities. This is especially true if your school is especially dedicated to student research or includes scholarly activity as a graduation requirement.

Senior Students

Speak with upperclassmen about their own research experiences. Having gone through the process themselves, they are a wealth of information. Not only can they tell you how they found their own project and mentor, but they may also be able to connect you with their own classmates who pursued projects in your field of interest. Other students are also a great way to learn more about the mentors themselves; just because a project was interesting does not mean that its

PI or research setting was enjoyable.

Medical School Website

Medical schools have a vested interest in making research opportunities that are available to students transparent, particularly for prospective students in the application process. Therefore, schools will details various pathways to academic work, either through curricular programs or by listing faculty members interested in working with medical students. Some institutions may also have searchable databases for research faculty and even available projects.

Symposia

As academic centers, most medical schools and academic hospitals will host speakers, conferences, and other academic conventions. These are a great way to network with the academic community and to learn more about who in the community is doing what work.

Listservs

Medical schools will often place their classes on email listservs for announcements. Mentors who are looking to work with medical students will often advertise opportunities or positions using such listservs.

Departmental Websites

If you are interested in a particular field, you can learn a lot about a particular department from their website. In addition to contact information, many departmental websites will also include recent publications and research interests of its faculty. Cold emailing is often great start.

Finding Summer Opportunities

Many students elect to pursue research opportunities during the summer after M1. If you are interested in finding opportunities at

your home institution, the above methods are likely your best bet. However, many students desire extramural summer experiences to learn more about other institutions or to engage in research projects that are otherwise unavailable at their home institution. Below are several methods for identifying suitable programs:

Your Home Institution

Summer research programs will share information with medical schools in order to advertise their opportunities and attract applicants. Speak with your administration to find out what extramural programs local students have previously participated in. Your administration may also forward such information and advertisements on your listserv.

The Association of American Medical Colleges (AAMC)

The AAMC maintains a database of research opportunities for US medical students. These range from summer programs to intensive year-long programs. These can be found at: **https://students-residents.aamc.org/attending-medical-school/research-and-training-opportunities/**

Such opportunities include:

- Clinical research programs
- Biomedical and basic science opportunities
- Public health projects and programs

Other Medical Schools

Much like your own institution, other medical schools will advertise research mentors and programs on their own websites. Peruse other schools' sites to see what programs are available, but make sure that such programs are available to outside students and are not solely reserved for their own

students.

Chapter 3

ETHICS: ETHICAL CONSIDERATIONS IN CLINICAL RESEARCH

ETHICS

Basic Ethical Principles

1. Research vs. Medical Care
2. Respect for Persons
3. Beneficence
4. Justice

Scientific Integrity and Public Perception

1. Public Trust and Confidence in Clinical Research
2. Reporting

3. Conflicts of Interest
4. Scientific Misconduct: Plagiarism, Fabrication, and Falsification

Voluntary Participation and Informed Consent

Privacy and HIPAA

Vulnerable Populations and Protections

Ethical Concerns: “Therapeutic Misconception,” Placebos, and Access

Section 1

BASIC ETHICAL PRINCIPLES

Three important documents were prepared in the 1900s that delineated the basic ethical principles that should be upheld in all clinical research activities. These three also included instructions for how to properly adhere to these tenants in clinical research projects.

DOCUMENT	YEAR	IMPO
Nuremberg Code[1]	**1947**	1. **Informed consent** must b 2. Research activities must a **harm** 3. **Potential benefits of rese**
Declaration of Helsinki[2]	**1964**	**1. Base research on scientif** **2. All planned research acti** **3. All protocols should be r** **(i.e. IRB)** **4. Assess predictable risks a**
		1. Discern medical practice **from medical research (d** **hypothesis testing)**

Belmont Report[3]	**1979**	**2. Research activities shoul human subjects** **3. Respect for persons, ben** **4. Respect for participant a** **5. Protection and respect fo capabilities and/or auton**

1. Research vs. Medical Care

Medical Care/Practice/Therapy

Intervention intended to improve the wellbeing of an individual

Safety and efficacy have previously been established and proven

Can reliably anticipate benefits of this intervention, which outweigh its known risks

Reasonable expectation of success

Medical Research

Activities intended to test a hypothesis

Will produce generalizable knowledge that will contribute to medical literature and practice

Described in protocol with objectives

Cannot reliably anticipate benefits, risks, or success

If Medical Research is performed in conjunction with Medical Care, you must explicitly state which elements are Medical Care and which are Medical Research!

Respect for Persons

- Respect the autonomy of all individuals and research participants
  - Allow them to deliberate and act on personal goals
  - Allow them to independently consider

whether or not to participate in research activities
    - All subjects must be allowed to participate voluntarily and withdraw at any time!
    - Individuals are allowed to choose what will or will not happen to them
- Present and share as much information about the research as possible so that they can make an informed decision
    - Allow time for consideration
    - Answer any and all questions
- Respect and protect those with diminished autonomy
    - I.e. the immature, the incapacitated, and the vulnerable
    - Protect those who are vulnerable from undue

coercion (i.e. prisoners)

3. Beneficence

- Do no harm
- Maximize benefits, minimize possible harms and risks
    - But in order to avoid harm, one must first learn what is harmful!
- Weigh all potential benefits against potential risks
    - Risks should be comparable in magnitude to benefits, but should always be less
    - Consider the Risk/Benefit ratio

Justice

- Do not allow research participants to accept burdens unduly
- Equal distribution of benefits and burdens across society
- Equal access to research opportunities and benefits across society

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Section 2

SCIENTIFIC INTEGRITY AND PUBLIC PERCEPTION

Public Trust and Confidence in Clinical Research

The progress and success of clinical research and all human subjects research rests on the public's generosity and willingness to serve as human participants. It is therefore the responsibility and charge of those conducting research to honor the public and their participants by safeguarding the health and rights of all subjects, remaining transparent and objective throughout the research process, and making all results publicly available.[1]

The last few decades have seen a dramatic change in primary sources of research funding: 70% of all funding for new drugs research has come from the private sector while government support for research has declined. This has led to public concern regarding biases in clinical research efforts; does this present a potential conflict of interest in the reporting of results, publication, and treatment recommendations?[2] Such examples of include the exploitation of trivial difference between drugs, leading to the publication and recommendation of an otherwise redundant drug in peer-reviewed literature.[3] Several investigations into the literature have also suggested that investigators with ties to the drug company sponsoring their trials are more likely to produce favorable results.[4]

This does not mean that industry is inherently evil. In fact, the partnership between academia and the private sector is vital: the former provides novel investigations and treatments while the latter enables rapid translation of those studies into real, accessible interventions and knowledge. Since World War 2, public support for medical research has largely been attributed the public's belief that

scientific work will yield tangible benefits for not only the general population, but also for themselves. Such benefits include the national economy, national security, and healthy population.[5]

Despite the increasingly commercialization of biomedical research, there still exists a high level of trust in the realm of medical research and its investigators.[6] As of 2005, the public's perception and confidence in biomedical research is as follows:

High level of trust in public sector and university researchers

- Only two entities are trusted more: peer-reviewed journals and the World Health Organization (WHO)

High level of trust in public researchers

Growing awareness of the partnerships between public and private sectors

Growing awareness of patenting in public sector

- May compromise or erode public trust[6]

Without the public's trust, biomedical research will not be able to proceed unless supported by altruistic, willing volunteers and a favorable public at large. Therefore, biomedical investigators bear an ethical and moral obligation to remain transparent, objective, and unbiased in their endeavors. To garner and maintain public support, we must disclose all relationships, recruit an equitable population, record trial information in a public database, and share all human subjects research results with the public in a timely manner.

Conflicts of Interest

A conflict of interest (COI) may call into question the objectivity of any research being performed and the safety of its participants, and may represent a threat to the public's trust of biomedical research. A CoI may be financial (FCoI) or non-financial, and essentially includes any relationship belonging to an investigator which may influence his objectivity and ability to carry out and report

research ethically and according to scientific method.[5] Because of the increasing presence of the private sector in biomedical research, CoIs are "common and practically unavoidable in a modern research university"(2015).[7]

Non-financial Conflicts of Interest

These are usually not of overt concern and and not reported. In fact, they are often beneficial as motivating factors for investigators. However, their existence and potential effect bear reminding; these may also unduly influence and compromise judgement and objectivity as much as FCOI.[8]

Non-financial COI may include but are not limited to:

Career advancement

Peer recognition

Grant Application

Publishing

Financial Conflicts of Interest

Because of potential dangers of personal interest, institutions and peer-reviewed journals largely require that all investigators disclose any potential FCoIs and, if possible, to quantify these. Institutions typically collect this information annually and with every new IRB application, while journals require it with submission of publication materials. This was originally done to ensure the reliability of any data sent to the FDA related to new drug or treatment applications.[5]

Institutions and their IRBs review and consider FCoI information with the submission of each new study protocol/IRB application and during ongoing review of existing studies. This is done to ensure that is protocol is followed objectively (does an investigator stand to make money if this study provides positive results for the sponsor's drug?), safely (will the investigator put

participants at risk for unnecessary harm for personal gain?), and ethically (will the investigator forego the rights and welfare of their participants? It is also vital to confirm whether or not the sponsor has controlled the right to publish, i.e. the investigator cannot publish independently without the sponsor's review and consent.[9,10]

Financial COI may include:

Consulting Fees

Lecture fees (for giving a scientific lecture related to the sponsor's work or product)

Travel fees (for traveling to scientific conferences or professional meetings on the sponsor's dollar)

Serving on a sponsor's board or committee

Equity interests or stock

Gifts, honorariam, or services unrelated to the cost of research

When reviewing an investigator's potential CoIs in an annual financial disclosure, IRBs will look for any evidence of "significant financial interest" that may compromise the integrity of any of that investigator's current and proposed projects. If a CoI is considered to be of significance, an IRB will then reach out to the investigator, instructing them to manage, reduce, or eliminate that interest/relationship within 60 days.[2]

Managing a CoI may include limiting the conflicting investigator from aspects of the trial, such as removing them from study design, recruitment, obtaining informed consent, performing procedures, analyzing study data, and reporting safety information (AEs, SAEs). In short, the investigator should be removed from anything that their relationship could potentially compromise, especially with respect to subject safety. Management may be as drastic as assigning a separate, independent investigator to perform the study.[11,12]

Reducing a CoI means, quite literally, diminishing a quantifiable conflict. This usually means minimizing the price tag assigned to a service or relationship, such as consulting or speaking fees, paid lectures, stock, or royalties.

Eliminating a CoI means terminating a relationship altogether.

Reporting

Many volunteer to serve as participants in human subjects research because they believe that biomedical research will yield tangible benefits for both themselves and for the public. Therefore, it is expected that all results from clinical research will be reported and made publicly available, usually in the form of a peer-reviewed publication. This is done not only for the advancement of science, but also as part of the commitment made to research subjects; in bioethics, human subjects research is only justified if society as a whole gains knowledge and benefits from the sharing of results.[9]

The following is thus expected in the sharing, reporting, and publication of clinical research data:

Registration of any and all human subjects research before recruitment

- Ensures that public has access to trial information such as disease/condition studied, intervention, location, recruitment status, and results
- Allows for equal opportunity to participate (if currently recruiting)
- Enables increased accountability and transparency

Public sharing of new findings from ongoing human subjects research

- Particularly related to efficacy and safety

- Especially if results relate to safety or may affect a volunteer's willingness to participate

Disclosure of all funding sources and COI, including but not limited to:

- All relevant institutions and affiliations
- Both personal and financial COI
- Role(s) of sponsor in the project (in study design, collection, analysis, writing, etc.)
- Whether or not the investigator had full access to data
- The use of an independent statistician for data analysis in sponsored trials

Publication of all clinical research data within 12-18 months of completion

- No fragmentary publishing (i.e. publishing pieces of information from a project over time to garner more publications)
- All clinical trial results, whether positive, negative, or inconclusive

Scientific Misconduct: Plagiarism, Fabrication, and Falsification

Accusations of scientific misconduct are serious. The development and dissemination of medical research relies on publication and on the integrity of investigators, in whom the public places its trust in agreeing to voluntarily accept the burdens and risks of research participation to better science and medicine. Episodes of scientific misconduct undermine that very trust and call into question the validity of all biomedical research, its treatment of human subjects, and all results and recommendations.[15,16]

In 1999, the Royal College of Physicians of Edinburgh described misconduct at the Consensus Conference on Misconduct in Biomedical research as "Behaviour by a researcher, intentional or not, that falls short of good ethical and scientific standard." The Office of Research Integrity (ORI) in the US characterizes research misconduct as the following:

Fabrication: inventing data or results and/or recording them as research results and/or publishing them

Falsification: modification of research resources, equipment, or data results such that the research record is no longer accurate and true to events (includes the omission of results)

Plagiarism: use of another's ideas, procedures, methods, or worse without properly attributing them to their proper author (include self-plagiarism)[17,18]

*Research misconduct does not include honest error!

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Section 3

VOLUNTARY PARTICIPATION AND INFORMED CONSENT

An individual's choice to participate in human subjects research must always be voluntary and free from coercion. This is because all human subjects and biomedical research, much like all proven medical practices, interventions, and therapies, pose potential risks and burdens. But what separates research from established medical practice is two-fold:

The benefits, risks, and burdens of proven practices are known

-The benefits, risks, and burdens of research interventions or treatments can be predicted, but are ultimately unknown (and may be as severe as death)

1. **The usage of interventions and treatments in established medical practice are often required to improve conditions or alleviate suffering of patients**

-Participation in human subjects research is entirely optional and not otherwise necessary for the individual

Medical research relies on the altruism of the public to accept otherwise unnecessary burdens and risks in the hopes that their participation will produce generalizable knowledge and new, life-saving technique, procedures, and treatments.[1,2]

Elements of Informed Consent

It is therefore the responsibility of the investigator to safeguard not only the health and welfare of their research participants, but also

the participants' rights, namely that to voluntarily participate in human subjects research. Voluntary participation in human subjects research is indicated and documented in Informed Consent. This is the process by which an individual consents to enroll in clinical research and indicates that they understand the study, its design, its intentions, its potential benefits and risks, and its provisions. This process is captured in an IRB-approved Informed Consent document, which is legally effective and is signed by the investigative party, the consenting subject, and any witnesses.[3]

Informed Consent documents usually include:

- Title and purpose of research
- All institutions, companies, bodies, and investigators related to the research
    - Including relevant COI
- Findings from preliminary work (usually in basic science or animal models) or the literature which justify the research
- Foreseeable risks, benefits, burdens, or discomforts to subjects
    - Including any additional costs related to participation
    - May also include potential risks, benefits, or burdens to fetuses
- Alternative procedures that subjects may want to consider (in place of procedures offered in this research project)
- Extent to which subject confidentiality will be maintained (what personal information will be collected and who on the investigative team will have access to it)
- The approximate number of subjects to be enrolled

- Safety provisions in place for any risks or harm that may befall subjects in research
- Anticipated circumstances in which an investigator may withdraw a subject from the study
- Monetary or other forms of compensation offered to research subjects
- Assurance that participation is voluntary!
    - Subjects may withdraw at any time without any penalty or loss of benefits

Because of the weight of agreeing to participate in research, primarily because the subject is willingly exposing themselves to otherwise unnecessary risks and burden, it is tantamount that the consenting process is carried out ethically and is collected and documented properly.

Informed consent is generally broken down into three components:

<u>Information</u>

a. Sufficient information is given regarding the study (i.e. its purpose, treatment, procedures, study population, benefits, risks, etc.)

<u>Comprehension</u>

a. Study information is presented clearly and at the proper level for the intended study audience (i.e. is presented in basic language that can be understood by a non-scientific individual but is still informative)

<u>Voluntariness</u>

a. The subject makes the decision to participate of their own accord and is not subject to any coersion or undue influence and is not in a dependent relationship with the investigator

b. The subject is given adequate time to decide (time to read the consent, ask questions, consult family members, etc.)

c. Subjects should be reminded that they can withdraw at any point in the research without fear of consequence[1,3,4]

Execution of Informed Consent

When approaching potential subjects for inclusion in studies, investigators tend to detail the study and highlight aspects that may be relevant to the individual's willingness to participate orally. The individual will then read the informed consent document, free to ask the investigator any questions as they arise.

The investigator should remind the individual that participation is optional and voluntary, and that they are able to decline participation free of punishment or consequence. They should also be reminded that if they consent they are free to withdraw at any time. In no way should the investigator attempt to pressure or influence an individual's decision. When reviewing applications for new studies, IRBs will pay special attention to the compensation offered: it is possible that financial incentive may cloud an individual's judgment, pushing them towards unnecessary risk!

The individual should then be given as much time as they need in order to decide whether or not to participate. This may be as short as a few minutes to think to themselves, or as long as a few days in order to consult family. If they elect to participate, they should then sign, date, and time the informed consent document (if able). The member of the investigative team collecting consent will then also sign, date, and time the document, as will any witnesses or translators. If the individual is not able to physically or legally give consent (i.e. they are under 18 or their autonomy is diminished), the consent will be signed by a legal representative. In this case, the individual's assent should be collected and respected.

The subject should then be given a copy of the signed

informed consent form.[2, 3,5]

Exceptions to Informed Consent

There are several instances where standard informed consent is waived or bypassed, usually due to emergency situations (in research related to emergency situations, primarily for interventions) or because it is simply not possible to obtain. IRBs will often waive or modify the requirement for informed consent for practical purposes in the following circumstances:

Emergency Medicine Research: Incapacitated (whether temporary or not) individuals are not able to give informed consent. Therefore, IRBs will often waive the need to consent the following groups of individuals if their population is the object of study:

- Those with acute head or brain injuries
- Comatose patients
- Incapacitated, sedated, or unconscious patients
- Patients in life-threatening situations

In these instances, the IRB will generally require that the investigator is able to justify why consent needs to be omitted for this project, and will also require proof that this research will benefit the population that this individually represents (i.e. comatose or unconscious patients). There should also be evidence from prior studies which may suggest that this intervention/treatment will be beneficial for these groups of patients. In lieu of the participant's consent, consent will be either be waived or obtained from the participant's legal representative or proxy.[2,6-9] _

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Section 4

PRIVACY AND HIPAA

Health information privacy is firmly rooted in the principle of respect for persons. Investigators are charged with protecting and promoting the rights and interests of study subjects, which includes respecting the patient's autonomy and privacy. Health information records capture some of the most intimate details of a person's life: physical and psychological conditions, social history, and demographics. This may include information that is kept strictly between the physician and the patient out of fear of stigma, embarrassment, or discrimination.

Should a data set enable a reader, whether authorized or not, to identify individuals participating in a research study alongside their personal health information, those individuals' rights have then been compromised. It is therefore imperative that investigators respect the privacy of their volunteers by safeguarding personal data. The primary document providing instruction on the collection, storage, and use of Protected Health Information (PHI) is the Health Insurance Portability and Accountability Act of 1996 (HIPAA).[1-3]

Privacy and Confidentiality

Privacy generally refers to who has access to what PHI and when (who can look at my information?).

Confidentiality concerns trust in an interpersonal relationship in that certain information will be kept within the relationship and not disclosed to third parties (will my doctor tell anyone else what I tell them?).[4]

An individual's right to control who know what about them is vital to their personal autonomy, individuality, and dignity. Patients and especially research subjects place an incredible amount of trust in

medical personnel when disclosing HPI, which forms the basis of the physician-patient relationship. Without this trust, patients may withhold information that may be vital to their care. In the setting of clinical research, this translates into inaccurate data and an incomplete record, potentially skewing future analysis![5]

HIPAA and Handling PHI For Research Purposes

Protected Health Information (PHI)

Per the Privacy Rule under HIPAA, PHI is any information related to health status or healthcare utilization (including payments) that can be linked to an individual. In order to protect PHI, clinicians/investigators cannot usually use or disclose an individual's PHI without written permission (authorization) from that individual.

Obtaining and Collecting PHI for Research

In order to use PHI in a research study, written authorization must be obtained from individuals and is typically combined with informed consent (many IRBs include this language in informed consent templates). This is even true of retrospective chart reviews, though in many instances an IRB will grant a consent waiver (potentially consenting thousands of patients whose data is in a database would be time-consuming)

In protocols, informed consents, and with potential subjects, it is expected that investigators will:

State exactly what information is to be collected

Indicate how that information will be stored

Identify exactly who on the research team will have access to that information (and under what conditions)

Only collect as much information as is necessary to complete the research project (extraneous information will put the subject's privacy at a greater risk if identified)

When is Authorization Not Required?

Activities in preparation of research
  - i.e. chart review in order to develop protocols or evaluate enrollment potential for a future study or clinical trial
  - Information is reviewed solely for research project and no PHI is to be collected
  - This does not require IRB review

- Chart review of deceased individuals (authorization not required from legal representative or next of kin; waiver not required from IRB)
- Recruitment of an investigator's own patient (the IRB must approve of recruitment plans as outlined in the protocol; consent of that patient is still required for enrollment)
- Usage of deidentified information or a limited dataset (see next sections)

Deidentified Information

If data is stripped of all identifying features, or is deidentified, it is no longer considered to be PHI and is not protected under HIPAA. Therefore, authorization is not required to collect information from databases with deidentified information. The most common method for deidentifiying data, the "Safe Harbor" method, is described in HIPAA and requires the removal of the following 18 identifiers:

Names All geographical subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geocodes, except for the initial three digits of a ZIP Code, if	3. All elements of dates for dates directly related individual (including bi admission date, dischar death) and all ages over elements of dates (inclu

according to the current publicly available data from the Bureau of the Census: (1) the geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people; and (2) the initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people is changed to 000	indicative of such age, e ages and elements may into a single 1. Phone numbers 2. Fax numbers 3. Email addresses 4. Social Security Number 5. Medical record numbers 6. Health plan beneficiary 7. Account Numbers 8. Certificate/License num 9. Vehicle identifiers and including license plate n

However, there are often instances where access to this sort of information may be crucial to a research project, such as in demographic or epidemiological studies. An investigator may then opt to use a limited data set. A limited data set has only 16 identifiers removed, and can include information such as city, state, zip code, dates, and other numbers which may be crucial for a research project.[1,6]

Subject Identification Codes

Because of privacy concerns, it is often easier to assign

research participants unique subject identification codes in order to protect their identity. All study documents and records will refer to that subject by their assigned code instead of their actual name (this may also reduce bias in data analysis), except for two key documents: 1) the Informed Consent (signed by the subject) 2) a Subject Identification Code List, a confidential list linking subject identification codes to their corresponding identity.[1,7]

Encryption: Further Protection of Data

The use of encryption is recommended, especially in instances of theft or loss of external hard drives and laptops. Encryption is essentially reversible data transformation. Data is "translated" forward into a unique code, which is not legible or usable until it is translated back with the use of a key. This key is external to the encrypted data, and enables only authorized access to data.[1,6,8-10]

Protection of Genetic Information and Biospecimens

In an age of unprecedented computing power and increased digitization of biologic and genomic data, it is also important to protect genetic information and biospecimens (such as tissue and blood) collected from research subjects. It is theoretically possible to identify an individual from genetic information if their genomic information is known in another location, and biospecimens should be protected if they are associated with PHI. Federal law regarding these protections and when they are applicable is often confusing and ambiguous, but several concepts are key:

- Biospecimens, such as blood and tissue, are only protected if they are associated with PHI
- Specimen collection is considered human subjects research if it is collected as part of a research project (or is readily identifiable)
- Informed consent must be obtained before the collection, storage, use, or analysis or any biospecimens
    - UNLESS:

- The project poses no more than minimal risk to subjects
- The project does not affect the rights or welfare of the subject
- The research project cannot proceed if consent is required and not waived
- Subjects will receive additional information about the study after their participation

- Reminder: PHI cannot be shared or disclosed unless deidentified or is used in a limited data set[1]

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Section 5

VULNERABLE POPULATIONS AND PROTECTIONS

Per the bioethical principle of **respect for persons**, investigators are to respect the autonomy and right to self-determination of their research subjects. This principle is primarily realized in voluntary participation and in obtaining informed consent for all subjects. The NIH defines "**consent capacity**" as "an adult's ability to understand information relevant to making an informed, voluntary decision to participate in research." However, there are certain populations whose decision-making abilities or ability to exercise free will may be reduced, which leaves these population susceptible to coercion, manipulation, or harm by researchers. These groups are termed "**vulnerable populations**."[1,2] The following are generally considered to be vulnerable populations, but this list is by no means exhaustive:

Children and minors

- Not of legal age to give consent
  - "Developing," therefore are of limited cognitive and emotional capability[3]

Pregnant women

- Altered risk/benefit ratio; need to consider not only risks and benefits for the mother, potential risks and benefits for the fetus

Fetuses (conception to delivery)

- Not able to give consent[3,4]

Neonates (birth to 1 year of age)

- Not able to give consent[4]

Prisoners

- May be subject to coercion due to incarceration, or may consent out of false anticipation of benefits (reduced jail time, parole, etc.) or out of fear of punishment[3,4]

Members of hierarchical organizations (students, military, employees, etc.)

- May consent out of false anticipation of benefits (favoritism, promotion, etc.) or out of fear of punishment[3,5]

Those with impaired cognition

- Includes the mentally or emotionally disabled, the terminally ill, institutionalized individuals, and those with a neurological disorder (i.e. stroke, dementia, coma, etc.)

- Must have consent from legal guardian, and must re-consent the subject should they recover from their impairment and thus regain autonomy[3,4,6]

The socioeconomically disadvantaged

- Several barriers to equitable participation in clinical research: may be uninsured or underinsured, may not want to incur additional costs for medical services or additional hospital visits, may not want to be randomized in a study if in need of treatment, etc.[3,7-8]

However, to simply bar these groups from participating in research would go against the bioethical principle of **justice;** there must be equal distribution of resources and access to the benefits of research across society. Research must also include these populations so that they too are able benefit from medical advances related to relevant conditions. For instance, safety and efficacy data for SSRIs should come from studies whose populations include the mentally ill. Certain conditions or diseases are also uniquely confined to some of these populations, such as pediatric cancers or preeclampsia in pregnant women.[1,8,9]

Therefore, in order to ensure that their welfare and interests are properly respected, vulnerable populations receive additional protections and safeguarding measures if they are to be included in clinical research. The Declaration of Helsinki states: "Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research."[10]

IRBs will thus require specific, explicit justification for the proposed inclusion of a vulnerable population in a study. Additional regulations apply for studies including specific vulnerable populations:

Children and minors

- Requires consent of parent or legal guardian
- Children and minors may give assent in addition to parent or legal guardian's consent
- There should be minimal risk to the child (if more than minimal risk, there should be the potential for direct benefit to the child)
- Benefits should outweigh the risks

- The research, its protocol, and its procedures should be explained in a language that the child and parent(s) and/or legal guardian can understand
- The investigator must provide a justification as to why this project cannot continue without the inclusion of children and/or minors[4]

Pregnant women

- Study should be of direct benefit to pregnant woman or fetus
- There should be minimal risk to the fetus (if more than minimal risk, there should be the potential for direct benefit to the fetus)
- Trials may exclude woman of childbearing potential who are not on birth control due to potential risk to the fetus should she become pregnant during the trial[9]

Fetuses (conception to delivery)

- Must have consent from mother and father (if possible)[4,11]
- Investigators are not allowed to assess the viability of a fetus in a clinical trial
- There should be data from prior studies on pregnant animals or non-pregnant women to estimate potential risk
- There should be minimal risk to the fetus; all risks must be reduced

- Information related to the trial must be shared with and understood by the consenting parent(s)
- The investigator must provide a justification as to why this project cannot continue without the inclusion of fetuses
- There can be no inducement by the investigative team to terminate pregnancy[4]

Neonates (birth to 1 year of age)

- Must have consent from mother and father (if possible), or legal guardian
- There should be data from preclinical studies to estimate potential risk
- Information related to the trial must be shared with and understood by the consenting parent(s) and/or legal guardian
- Investigators are not allowed to assess the viability of a fetus in a clinical trial[4]

Prisoners

- A "prisoner advocate" must participate in the consent process and all related IRB determinations
  - Prisoner advocate: someone familiar with prisons who is unrealted to the prisoner
- Both the prisoner and the advocate must

understand the research, including its risks and benefits, and sign the informed consent

- The prisoner cannot be promised any additional/special treatment or reward (such as earlier parole, release, etc.)
- The prisoner must be available for all follow-up visits related to the study protocol[3,4]

Members of hierarchical organizations (students, military, employees, etc.)

- Declining to consent should not affect the individual's career or credits. IRBs will ensure that organizations do not pressure members into research participation.[3,5]

Those with impaired cognition

- Must have consent from legal guardian, and must re-consent the subject should they recover from their impairment and thus regain autonomy[3,4,6]

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Section 6

ETHICAL CONCERNS: "THERAPUETIC MISCONCEPTION," PLACEBOS, AND ACCESS

"Therapeutic Misconception" and Research vs. Care

Individuals volunteering to participate in clinical research typically cite a variety of reasons for doing so, such as altruism, wanting to contribute to the advancement of science, or the personal need for therapeutic benefit. However, many subjects fail to understand that clinical trials are not necessarily designed to be of benefit to its subjects, but are instead intended to provide data years out from the trial to better inform the care of future patients with the same conditions; the treatment or interventions being tested on them are to be used in future generations. This is referred to as the "**therapeutic misconception**".[1,2]

This is best demonstrated in Phase I trials for new cancer drugs, which are designed to evaluate a range of dosages and determine which is the least toxic and most efficacious. This is usually evaluated in a small group of healthy volunteers. The purpose of this pool of individuals is to determine a safe dosage that will be evaluated for efficacy in Phase II and III trials; Phase I is strictly "safety," while later trials will be aimed at determining actual activity.[2] Despite the informed consent process, many subjects in Phase I trials fail to understand that investigators' intention is not to treat, but rather to determine what dosages can be tolerated by humans. It may not be clear to subjects that this is the first time that

this drug is being tried in humans, and therefore may bear unpredictable, toxic effects. Some subjects in a Phase I trial will receive dosages too low to show any effect, while others will be exposed to incredibly toxic, even potentially fatal levels of the drug.[3]

It is important that investigators are aware of this when approaching potential volunteers for inclusion in clinical research projects.[4] While it is the intent of informed consent to best educate subjects on the goals of research, many still consent to research out of hope for their own condition. These intentions should be made clear to respect the autonomy of subjects and to protect them from potential exploitation. This is especially true in interventional trials for life-threatening conditions, such as cancer, where potential subjects may be especially vulnerable and research drugs may have an undetermined risk/benefit ratio.

It is therefore important that investigators, as well as their research subjects, fully understand the **differences between research and treatment.**[5] The goal of *treatment*, or care, is to benefit an individual using proven, standard methods. The goal of *research* is answer a scientific question, usually related to a disease process or intervention, which will better inform *treatment* for future generations. For instance, many research subjects will not understand that some diagnostic tests included in trial protocols are used only to provide study data. Though some of these tests or procedures may normally be included in routine treatment, their results in the trial may not be used to better inform the subject's treatment.[6] Subjects may not even be aware that they may be charged for these study-related procedures.

Randomization and Use of Placebos in Research

Though the concepts of subject randomization and placebo treatment are commonplace and even the gold standard in modern clinical research, both bear significant ethical concerns, especially in light of "therapeutic misconception."

Randomization

In randomized controlled trials (RCTs), subjects are randomly assigned treatment in order to reduce internal variability. Randomization seeks to account for confounding factors that may impair an investigator's ability to properly reach scientific conclusion.[7] This effect may be enhanced by *blinding*, in which either the investigator or subject is prevented from knowing which treatment has been assigned and administered, reducing bias and subject/investigator interference. *Double-blinding*, keeping treatment identity from both investigator and subject, further enhances this effect.[8,9]

Critics of randomization have identified several ethical issues:

- Depending on study design, subjects not randomized to active treatment may forego or not receive individual treatment related to their condition.
- Those who accepting the risks and burdens of clinical research are not the individuals who seek to gain from it.
    - Trial data will be used to inform care of future patients, i.e. those not currently in the trial. It is not the intention of research to treat or cure its immediate subjects.
    - Investigators, institutions, and sponsors may benefit from research, either professionally or financially, while subjects will not.
- During the course of a clinical trial, early evidence may show that one treatment is superior.
    - This then indicates that subjects in other treatment groups are receiving inferior care by not receiving the most efficacious intervention.
    - It is then the ethical responsibility of the

investigator to make the superior treatment available to all subjects and to communicate these findings to the medical community.[9-12]

Placebos in RCTs

There are several trial design methods that can be used to elucidate the activity of study drugs. Investigational drugs can be compared to the standard treatment for that particular condition in **active-controlled trials**, or can be compared to the effects of not receiving that treatment in **placebo-controlled trials.**

To date, placebo-controlled RCTs are the gold standard in clinical research because they:

- Eliminate both investigator and subject bias (other than therapeutic activity, placebo formulation is identical to active)
- Provide a "zero-point reference" to compare treated vs. untreated progression of disease or condition
- Easier to show statistical significance
- Spare control population from potentially toxic effects of active treatment[9,12,13]

However, the use of placebos presents several disturbing ethical dilemmas:

- Inherent deception of subjects by investigators
  - Subjects are told at time of consent that they will not be told which treatment they are receiving
  - All subjects will be treated as if they are receiving active treatment in order

to reduce bias and control for placebo effect.

- Potential risk: subjects may be harmed by not receiving active treatment
    - Disease or condition may progress; risk for higher levels of pain or even death[9,14,15]

The usage of placebo in clinical research is thus largely reserved for two unique circumstances:

- There is no standard, accepted treatment for the disease/condition (and therefore nothing to compare study drug to)
- Standard, accepted treatments for the disease/condition are only partially effective or have serious side effects[12,16-19]

It is ethical to use an **active-control** should a standard therapy exist so that subjects not assigned to active treatment still receive standard care for their disease or condition. This model is not without its own unique issues, such as what happens if a test drug is shown to be as effective as standard treatment. Two conclusions are possible:

1. Both drugs were effective in the study population
2. Neither drug was effective

Critics have noted that, without a placebo, trials may lack "internal validity." There may be certain circumstances in which a placebo-controlled trial may still be warranted even when there is an accepted standard of care. These are of particular interest to drug companies who may want their own entities tested even when an analog exists:

- The study drug may potentially pose fewer side effects or risks to subjects than standard treatment

- Study drug may benefit those who are allergic to standard treatment
- Study drug may benefit specific populations that standard treatment does not[5,18-20]

Access and Representation in Clinical Research

It is important that access to clinical research opportunities is as equitable and fair as possible. This is not only to ensure that the risks, burdens, and benefits are fairly distributed across the population, but also to ensure that data obtained from clinical research is *applicable* to the entire population. A limited study cohort that is not representative of the entire population that is at risk for a certain disease or condition will skew the interpretation and application of that study's results; a study drug may exhibit variable efficacy, toxicity, and side effects across different populations.

A team of congressional investigators observed in 1990 that most of the data concerning research and human health is derived from white men. It was observed that clinical research seldom includes women or minority populations. It is imperative to include a variety of subjects in clinical research to account for potential differences across population, such as hormonal differences between sexes or genetic variation. The success of medical research relies on the altruism of its volunteer subjects who accept otherwise unnecessary risks and burdens in order to benefit society at large. Society's participation in the research machine is only justified if potential benefits are maximized, so it is the responsibility of investigators to ensure that their research pool is as diverse and inclusive as possible.

Though there are obvious instances where a limited research cohort is justified (i.e. a Phase II trial for a pregnancy-related medication excluding men), it is otherwise a direct violation of the bioethical principle of beneficence to enroll an exclusive group. It is potentially dangerous to base treatment recommendations for an entire population when all of the data was obtained from a subset of the population. For instance, lithium dosing was largely based on studies in white men. This failure in inclusion and enrollment is

ultimately harmful and contributes to bias in the medical literature and knowledge base. It also hinders the external validity of a study, rendering its results and recommendations not generalizable. Investigators are thus obligated to ensure a diverse and robust study population, which may require extra efforts and costs in order to include minority populations.[21,22]

Equitable distribution of research benefits is an especially poignant topic in the realm of international research, especially in collaborations between developed and developing countries. Populations in developing countries are inherently vulnerable because they have fewer treatment options and heightened barriers to healthcare. It is therefore important to avoid exploitation when studying an intervention in developing countries, especially when the primary benefactor of that research is the sponsor's country and not the developing country. This represents an uneven distribution of the risks and benefits of research: the developing country assumes the burdens of research, while the sponsor's home country will eventually have access new treatments. Therefore, investigators are ethically obligated to share the benefits of research with its collaborating countries under the concept of "Fair Benefits."

- Research should address health problems relevant to the developing country
- Research and protocol objectives must justify the inclusion of vulnerable population(s)
- The research must pose few risks, or the potential benefits must outweigh the risks
- If the study drug is found to be effective, the study drug should be provided to the developing country at the sponsor's expense at completion of the trial[12,23-27]

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Chapter 4

PROTOCOL

Sections

Institutional Review Boards

Initial Protocol Review

Continuing Review

Protocol Modifications/Revisions/Amendments

Serious Adverse Events, Protocol Deviations, and Reportable New Information

Section 1

INSTITUTIONAL REVIEW BOARDS

Under the Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects, review was established as a precondition to medical research. This article stipulates that any biomedical or behavioral research is subject to review by an independent Institutional Review Board (IRB) which will ensure that the rights and wellbeing of study participants are protected.[1] IRBs are typically established by institutions and hospitals and will review and monitor all research activities involving human subjects. It is therefore the charge of IRBs to ensure that all research projects are conducted ethically and that all study participants are respected and treated justly.[2]

IRB Structure

At least 5 members with varying professional backgrounds
Membership must be diverse

- Consider race, gender, cultural backgrounds, community attitudes
- IRB members may not be exclusively one gender
- IRB members may not be exclusively one profession
- IRB must include:
  - At least one person of a non-science background
  - At least one person of a science

background
    - At least one person not related to the institution
- IRB may want to include members of vulnerable populations, especially if those vulnerable populations are frequently subjects of research at that institution[1,2]

IRB Function

Review, approve, modify, or disapprove research
Notify all investigators in writing of all decisions
Review study protocols, informed consent documents, and modifications to existing research projects
Meets regularly; meeting dates are publicly available
- Usually twice a month

Decisions are made by vote
- By board members attending that meeting
- Must have majority vote

Review existing research projects at appropriate intervals
- Investigators must "renew" existing projects, typically annually
- Frequency of renewal relates to degree of risk

"Expedited review" is available
- For projects of minimal risk (i.e. chart review)
- For minor changes to existing project
- Usually carried out by one individual instead of entire board
    - Projects cannot be disapproved under expedited review

IRBs may call in "experts" to provide expertise on certain research topics
- "Experts" may not vote at board meetings[1,2]

What does this mean for me?

The IRB is a committee that will review all human subjects

research. IRBs are the "gatekeepers" of clinical research and exist to ensure that all clinical research activities are ethical and properly justify the inclusion of humans.[3] Essentially, an IRB must review all research protocols and materials. Research cannot begin and these materials cannot be used until an IRB gives full approval. All communications with IRBs, including sent messages, received messages, and all associated attachments, must be saved. The PI must sign off on all materials.

When to communicate with the IRB:

- Initial Protocol Review
- Continuing Review
- Protocol Modification/Revision/Amendment
- Protocol Termination
- Reportable New Information/Unanticipated Event

What to do with IRB communications

All IRB communications related to a project must be saved.[4] This is usually done in a study binder with a tab related to IRB communications, or split amongst several tabs: one for IRB submissions (things you send to the IRB) and one for IRB approvals. The entirety of each communication must be included! For instance, in the case of studies with recruitment materials, all study attachments sent to the IRB should be included with that communication under "IRB Submissions" and the returned, IRB-approved versions (usually with an IRB approval stamp) should be in the "IRB Approvals" tab. This may result in a lot of paper, so it may be useful to create a separate binder for study-related IRB communications. This binder should be labeled with the project title, protocol identification number, and with the PI. The IRB communications tab should contain a note indicating where IRB-related communications can be found (e.g. the IRB communication binder for the study).

References

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Section 2

INITIAL PROTOCOL REVIEW

DEFINITION

Submission of study materials, including all related forms and investigator information, to the IRB for approval to begin the study. This is usually your largest submission to the IRB. Most IRBs will have a checklist of required information and documentation on their websites. Some IRBs will allow submission via online portals (e.g. IRBNet), while others may simply use email. Most interventional research projects require **full committee review**, so turnaround time will depend on the committee's meeting schedule and may take over a month.[1] Some research projects will receive an **expedited review** and may be approved sooner. IRBs may either **approve, disapprove, or request a modification** of a protocol.

REVIEW TYPES

The study design will largely dictate the type of review a protocol will receive and therefore how long it will take to receive approval. The IRB will ultimately decide what kind of review is appropriate; this cannot be determined by the investigative team.

Exempt: Study presents little or no risk to subjects; usually relies on existing data (medical records, pathological specimens, etc.) that are de-identified. There are six categories receiving exemption:

1. Normal education practices (e.g. evaluating new instructional strategy, UNLESS students are randomized)

2. Anonymous educational tests, surveys, or interviews (UNLESS subjects can be identified)

3. Educational tests, surveys, or interviews where subjects can be identified, but they are public candidates or if confidentiality is protected by federal statute

4. Study of existing data (if publicly available or de-identified; subjects cannot be identified even indirectly or with demographic information)

5. Public benefit/service programs (e.g. Medicaid, welfare, etc.)

6. Taste and food quality evaluation (food cannot have any potential risk to consumers)[1]

Expedited: Study presents no more than **minimal risk** to subjects and a full committee review is not indicated. Review is thus performed by one or more IRB members, but not the entire committee. Retrospective or prospective evaluation of data collected under routine medical care usually fall under this category (e.g. **chart review** or specimen collection, as long as confidentiality is maintained).[1]

Per the FDA: *"'Minimal risk' means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."*[2]

Full: Research activities include the collection of data through interaction or intervention with human subjects and the use of identifiable private information.

PREPARING FOR SUBMISSION

Because of the size and turnaround time for the initial

submission, it is essential that your submission is as comprehensive and polished as possible. Remember, it not a given that your project will be approved and the IRB may request modifications to your study before giving approval.

- Review clinical research ethics to ensure that your study will ensure the safety of subjects and protect their rights
    - Be sure that the literature and all previous work clearly justifies your rational and research design, particularly the Inclusion/Exclusion Criteria

- Collect copies of all training materials for your investigative staff and be sure that they are up to date
    - CITI Training, institution-specific training, signed CVs, and medical licenses (if applicable)

- Follow your IRB's checklists for submitting new protocols to ensure that you are submitting all required documents. These will usually include:
    - New protocol application form (signed by PI)
    - Research protocol
    - Informed consent document or waiver (if applicable)
    - Recruitment materials, including ads and letters (if applicable)
    - Signed CVs, medical licenses, and valid CITI/ethics training for all investigative staff

- Data collection forms (case report forms or "CRFs")
- Surveys or questionnaires to be filled out by subjects
- Scripts[1]

SUBMISSION

Most IRBs now require electronic submission of all materials. This can be done in an online portal, such as IRBNet, or may be done by emailing all materials. Check with your local IRB to find out which method is locally preferred. Retain copies of all submission materials (including the email sent, if your IRB prefers that method of communication) in your IRB Communications/Submissions section in your study binder.

IRB RESPONSE

The time it takes for the IRB to respond depends on the type of review assigned to your study and when the IRB is scheduled to meet. Most IRBs will indicate their meeting times online.

Usually, one member of the IRB will review your submission first in order to address any immediate issues so that the investigative team may correct these before the IRB meets. Any requested modifications should be made apparent. As with any study modifications, even after IRB approval, this is usually done by submitting two versions of materials:

- One copy with "Tracked Changes" on so that all modifications to the protocol and other materials are made apparent
- One copy with "Tracked Changes" off and with all changes accepted to serve as the final, updated version

After review, the IRB will communicate one of 3 responses:

- **Approval**
- **Approval upon receipt of request modifications**
- **Deferred or tabled (requires substantial clarification, modification, or discussion)**
- **Disapproval**

Assuming the study is not disapproved, the IRB will assign the study a unique study identification number. This number should be applied to all study documents, including the protocol, recruitment materials, consents, study binders, and IRB submissions. *The IRB will also indicate when its approval expires and thus when continuing review is required.*

Again, remember to maintain records of *all* communications with the IRB, including emails and IRB submissions. This should be done both electronically and in the study binder.

References

1. Bankert EA, Amdur RJ, Amdur RJ. Institutional review board : management and function. 2nd ed. Sudbury, Mass.: Jones and Bartlett; 2006.

2. CFR - Code of Federal Regulations Title 21; Part 56 - Institutional Review Boards. In: Food and Drug Administration DoHaHS, ed. 21: U.S. Food and Drug Administration; 2016.

Section 3

CONTINUING REVIEW

After initial approval, IRBs will indicate when its approval will expire. Upon expiration, *all study activities must cease!* This includes any ongoing activities, including recruitment and following already-enrolled subjects. Therefore, to maintain continuous approval, the investigative team must submit "continuing review" materials to the IRB to ensure that study activities do not come to a halt. In their initial approval communication, IRBs will usually indicate when to submit for continuing review in advance of the expiration date to ensure that research is not interrupted.

PREPARING FOR SUBMISSION

Much like with the initial submission to the IRB, most IRBs will provide checklists and forms for continuing review. All materials that were previous reviewed by the IRB, especially those with IRB approval stamps (such as recruitment ads), will need to be resubmitted. They will also ask for updates from the previous approval period, including:

- Enrollment status
- Study milestones achieved
- Results from interim data analysis (if applicable)
- Reports from monitoring or audits
- Adverse events and their determined relationship to the study intervention and/or protocol[1]

IRBs will also ask what the current status of the study is.

Potential responses include:

- Research is permanently closed to enrollment of new subjects
- All subjects have completed all study-related visits and treatments
- Study is only open for long-term follow-up of previously enrolled subjects
- Remaining study activities are limited to data analysis[1]

SUBMISSION

Submit all required materials per your IRB's preferred method, either by portal (e.g. IRBNet) or by email. Retain records of all materials sent, including attachments, in your study binder.

IRB RESPONSE

Much like the study team, IRBs do not want approval periods to lapse. If you submit all required materials by the continuing review submission date previously indicated by your IRB, you should receive approval before the study expires. This will then come with a new expiration date and newly stamped materials. All materials stamped with the previous expiration date, such as recruitment ads, should be replaced immediately.

As with initial review, the IRB may reach out to you with queries or requested modifications. Again, remember to maintain records of *all* communications with the IRB, including emails and IRB submissions. This should be done both electronically and in the study binder.

References

1. Bankert EA, Amdur RJ, Amdur RJ. Institutional review board : management and function. 2nd ed. Sudbury, Mass.: Jones and

Bartlett; 2006.

Section 4

PROTOCOL MODIFICATIONS/REVISIONS/AMI

After initial approval of your study protocol, it may be necessary to modify aspects of your study while research is underway. Your IRB may refer to protocol changes as "modifications," "revisions," or "amendments." Modifications may relate to:

- Study personnel and roles
- Recruitment strategies and materials
  - Elements of study design (number of subjects to be enrolled, number of study visits, etc.)
  - Questionnaires, surveys, or other data collection forms

Modifications cannot be implemented until they have received explicit IRB approval. You must proceed with what has been previously approved until your requested changes have been approved by the IRB.[1,2]

PREPARING FOR SUBMISSION

As with initial and continuing review, IRBs will provide forms for changes to protocols. You must indicate what is being changed and provide proper justification.

If there are changes to previously approved materials, such as the protocol or recruitment materials, you must submit two versions

of these:

- One copy with "Tracked Changes" on so that all modifications to the protocol and other materials are made apparent
- One copy with "Tracked Changes" off and with all changes accepted to serve as the final, updated version

If you are requesting to add new study personnel, you must submit proper certifications for these individuals as if they were a part of the initial submission. This includes:

- Signed CVs
- Medical licenses (if applicable)
- CITI/ethical training documentation

SUBMISSION

Submit all required materials per your IRB's preferred method, either by portal (e.g. IRBNet) or by email. Retain records of all materials sent, including attachments, in your study binder.

IRB RESPONSE

If new materials require the IRB stamp, such as with a recruitment ad, replace all previous versions with the newly approved edition.

As with initial and continuing review, the IRB may reach out to you with queries or requested modifications.[1] Again, remember to maintain records of *all* communications with the IRB, including emails and IRB submissions. This should be done both electronically and in the study binder.

References

1. Bankert EA, Amdur RJ, Amdur RJ. Institutional review board : management and function. 2nd ed. Sudbury, Mass.: Jones and

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Section 5

SERIOUS ADVERSE EVENTS, PROTOCOL DEVIATIONS, AND REPORTABLE NEW INFORMATION

In order to protect the safety and wellbeing of human subjects in an IRB-approved study protocol, certain events must be reported to the IRB as they occur. If a study concerns an investigational new drug or procedure, the FDA must also be informed immediately under the study's IND.[1] If the PI is not the study sponsor (i.e. there is an outside sponsor, such as a pharmaceutical company), the third-party sponsor must also be informed. These events cannot simply be reported at the time of renewal. In light of this new information, the IRB and FDA can then re-evaluate whether or not this represents an increased risk to subject and if the study can continue.[2]

For instance, such events may include sudden medical or health developments in subjects, and it may be determined that such an event bears a causal relationship to the study intervention. The determination by the IRB, FDA, investigator, and medical monitor will depend upon the severity and frequency of such events, as well as if any causal relationship can be identified.

While such events are often perceived as "negative," such as when harm befalls a subject or when the protocol is not followed, they can also be positive: if early evidence indicates the superiority of a test drug or procedure, the IRB may end a trial early because it is no longer ethical to randomize subjects to an inferior treatment.[3] For the sake of transparency and subject protection, all such events must be

reported to the IRB, regardless of whether it is because of an investigator error or unanticipated occurrence.

Such events include:

Serious Adverse Events

Note: You must first discern **Adverse Events** from **Serious Adverse Events.** Only **Serious Adverse Events** must be reported immediately to the IRB.

Adverse Event (AE): defined as an unfortunate medical development that occurs during treatment with a drug, regardless of the event's relationship with the test pharmaceutical.[2] While this may be as mild and unrelated as a subject developing a cold during winter while enrolled in a trial, all such events must be recorded. AEs that are not Serious Adverse Events (SAEs; see blow) do not need to be reported immediately to the IRB and are usually captured in an AE log, which is submitted at renewal. The event must also be noted in the subject's chart, usually in a subject-specific AE log.

The PI of the study is required to determine whether or not a causal relationship exists between the event and study information. Remember: anticipated and expected AEs, based on existing and preclinical data, should be detailed in the study protocol and consent. If such events happen in more than one subject while enrolled in a trial, analysis may suggest a causal relationship with the test drug (this is how drug companies identify potential side effects). All events should be followed up on until resolution (e.g. query patients regarding previously reported adverse events to record date of conclusion/resolution and any sequelae in the adverse event log).

An IRB will usually require the following regarding an AE:

- A description of the event
- Start date
- Stop date (if no longer continuing)

- Severity (Mild, Moderate, Severe)
- Serious? (if so, must report ASAP to IRB as SAE- see below)
- Study drug relationship (not related, possibly/probably related)
    - Action taken with test drug (none, temporarily discontinued, permanently discontinued, dosage change)
    - Outcome of AE (resolved without effects, resolved with effects, ongoing, death, unknown)[2]

Serious Adverse Event (SAE): defined as any unfortunate medical event which:

- Results in death
- Is life-threatening
- Results in hospitalization or extends an existing hospitalization
- Results in prolonged/profound disability or incapacity
- Results in congenital anomalies or birth defects in a neonate

Because of their severity, these events must be reported to the IRB ASAP. Depending on the nature of the study, the FDA and/or sponsor must also be informed. IRBs may differ in reporting requirements, with some requiring notice within 5 days of the investigator being notified of the event or even within 24 hours. If the study is under an IND, the FDA must receive an IND safety report within 15 days, or within 7 days if it concerns an unexpected fatal or life-threatening reaction.

IRBs may vary in their SAE reporting forms, but all generally capture the same information:

- Subject ID
- Site of event (local- at test facilities vs. external)
- Unexpected or occurring at a frequency/severity greater than expected
- Possible relation to the subject's participation in this study
- Does this suggest that other subjects are also at greater risk?
    - If so, what changes will be made to protocol, consent, etc.?
- Was the sponsor informed?
- Other relevant documents (hospital records, death certificate, etc.)[2]

Note: A high frequency of SAE reports may trigger an audit by the IRB or FDA.

Protocol Deviations

Protocol adherence is critical for subject safety and scientific integrity. Any divergence from the agreed-upon, IRB-approved protocol is also a direct violation of Good Clinical Practice and FDA regulations. Therefore, any changes to a previously approved protocol must be approved by the IRB before implementation. A **protocol deviation** is an unapproved change in protocol activity that does not increase risk to subjects and does not compromise integrity or validity.[4]

Protocol deviations may originate from study subjects or

members of the study team and are often accidental. Failure to complete elements of the protocol also constitute deviations. Deviations may be identified by the study team or may be discovered by a monitor during an audit. The latter situation may be particularly serious because it negatively reflects on the study team and local IRB.

Examples of deviations may include:

- Subject's refusal of a blood draw indicated for that protocol visit (when protocol indicated that a blood draw would be performed at that visit)
- Failure to schedule a study visit within that visit's window (when the protocol indicated that the visit must be within a certain amount of days of target date)
- Documenting specific elements physical exam instead of a complete physical exam (when protocol indicated that a complete physical exam would be performed, but either a targeted exam was documented or a complete physical exam was performed and only specific information was documented)[5]

Deviations should be reported to the IRB and FDA immediately. Each IRB will have its own reporting timeline and requirements. **It should be noted that, in case of emergency, avoiding a deviation is secondary to immediate care**.

Note: The FDA treats all protocol deviations as violations (see below).

Protocol deviations break down into noncompliance, misconduct, and fraud. As noted by Ghooi. et al, a single instance of a deviation may be considered to be non-compliance, whereas several instances of the same deviation may be considered misconduct. Repeat deviations may end in suspension or early termination of the study by regulatory agencies (IRB, FDA, etc.)[4]

Protocol Violations

A **protocol violation** is a protocol deviation that increases risk to subjects or which compromises the study's scientific integrity.

- Failure to properly obtain and document informed consent
- Enrolling against the Inclusion/Exclusion criteria
- Mishandling study drug (not giving assigned drug, not storing properly, not documenting dispensation/return, etc.)
- Failure to report a SAE
- Falsification

Like protocol deviations, protocol violations must be reported to the proper regulatory authorities (i.e. IRB, FDA) ASAP. Excessive protocol violations may trigger an audit by regulatory authorities or termination of the study. Protocol violations are a serious offense and it is the investigative team's ethical responsibility to avoid and prevent them.

Reportable New Information

New information obtained during the trial may indicate a change a change in the risk/benefit ratio for subjects, or may affect a subject's willingness to participate or continue participation. "New information" may be a new publication related to the study, trends identified in interim data analyses, or the results of a recent Data Safety and Monitoring Board report (see below).[2] It could also be a change in the marketing approval for a study drug or device or a subject's complaint. Adverse events reported during trial participation may represent information that may affect a subject's willingness to participate is often a. Such information may be observed and shared by the investigator, the medical monitor, or the sponsor.

As with SAEs and protocol deviations, individual IRBs will have

their own reporting protocols and requirements for reportable new information. The IRB should be informed ASAP so that it can review new findings to determine whether or not the study requires modification, suspension, or early termination. However, such a development is not necessarily negative; data analysis may indicate adequate efficacy and safety of a drug relatively early into a trial. If so, it would be unethical to continue to randomize subjects to an inferior drug. In this case, a study would be terminated early because efficacy was demonstrated early, and not because of any incident, harm, or error.

Larger studies, particularly RCTs, are often governed by an independent Data Safety and Monitoring Board (DSMB).[2] These meet at least annually to review current data and recommend either continuation, modification, or termination of a study. These groups will then issue a report of its findings to all participating study sites. The investigative teams at these study sites must then submit these reports to their IRB. The PI of the entire RCT, or the individual holding the study's IND, must also inform the IRB. Audit reports, findings, and resolutions must also be submitted.

References

1. United States. National Bioethics Advisory Commission. Ethical and policy issues in research involving human participants. Bethesda, Md. (6705 Rockledge Drive, Suite 700, Bethesda 20892-7979): National Bioethics Advisory Commission; 2001.

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Chapter 5

PREPARING FOR RESEARCH

Sections

Training

The Research Question

Conducting a Literature Review

Choosing a Study Design

Writing the Research Protocol

Writing the Informed Consent or Waiver

Section 1

TRAINING

Though every institution and IRB will differ in specific requirements, participation in clinical research activities will require a degree of ethical and professional training. This training must be documented, with copies of all certifications in each study file that you are related to. You will also need to update and be re-certified in certain domains every few years, particularly in research ethics.

Ethical Training

Institutions will require that researchers are familiar with and understand clinical research ethics. The NIH has required this of all investigators for the protection of study volunteers since 2000.[1] This is typically done in the form of **CITI Training.**[2] The Collaborative Institutional Training Initiative (CITI Program) provides online courses in research ethics, responsibility, and conduct. The program can be found at https://about.citiprogram.org/en/homepage/ and offers over 70 courses related to clinical research. Most IRBs will at least require the Human Subjects Protection course, also known as the **Basic Course**

Getting Started with CITI

Find out which courses your local IRB requires. This can usually be found on its website. You can also ask IRB personnel or other members of your study team.

Go to https://about.citiprogram.org/en/homepage/ and click "Register" at the top right of the homepage. This will allow you to create an account.

Select your IRB/institution. This will ensure that courses your institution is specifically interested in will be displayed to you.

Complete the remaining steps to create your account.

Taking Courses with CITI

The courses made available to you on CITI are dependent upon your institution. While some institutions may pay for and subscribe to a wide range of courses, some may only use a select few. Courses typically take a few hours and consist largely of reading and quizzes. The quiz passing rate is usually around 80%, and these quizzes can be retaken as many times as needed to pass. It should be noted that, if retaking a quiz, the questions and/or answer options may be regenerated; you may never see the "same" quiz twice.

Some courses may also have "modules." These modules are comparable to elective. For instance, in addition to required material for all students, the remainder of a course may be comprised of selecting two out of eight possible topics to receive additional training on. Which modules you select are not mandated, and can be chosen based on individual interest or need.

Completion of a course will generate a certificate. Some IRBs will automatically receive a copy of this certificate, while others may require you to submit a PDF. These certificates should be saved. Every study that you work on will require documentation of training, AKA copies of these certificates.

The Basic Course

This course will take roughly 4-6 hours can be done over several sessions. You will review several important tenants and documents related to human subjects research, including the Belmont Report. Many of these materials and concepts are reviewed in this iBook under the ethics chapter. **It should be noted that this iBook is not a replacement for CITI training!** It should serve as a reference.

Other Courses of Interest

You may be required or interested in taking additional CITI courses, depending on your role in clinical research. Some noteworthy CITI courses include:

- Conflicts of Interest (COI) Basic
- Good Clinical Practice (GCP) for Clinical Investigation/Trials
- Data Security and HIPAA Training

Refresher Courses

Each training certificate you receive will come with an expiration date determined by the course and your institution. Before your training expires, you must be re-certified. Luckily, this does not require that you retake an entire course. Instead, every course has a complementary "Refresher" course. Refresher courses tend to be much shorter than the original course and are designed to ensure that you are still familiar with the topic. They may also include updates to the curriculum. These are also followed by a quiz. Completion of a Refresher course will also generate a certificate, which should be shared with your IRB and included in study files.

Educational and Professional Training

All members of the investigative team must demonstrate adequate qualifications to conduct a study. While individual requirements depend on each member's role, at least a Curriculum Vitae (CV) is required for all staff members.

Curriculum Vitae (CV)

CVs should be signed, dated, and included in all study files alongside CITI and other professional training. CVs should be updated to reflect positions, responsibilities, roles, and relevant publications.

Medical and Professional Licenses

Physicians and nurses participating in the research study must

provide copies of valid licenses to practice in the study documentation. These assert that these individuals are properly qualified to serve in medical capacities during research activities.

Study-specific Training

Because the integrity of clinical research data and the safety of subjects depends on proper conduct, it must be demonstrated that research staff members involved in these activities are properly trained. Such training may be documented in a **Training Log**, which are often required in multicenter clinical trials. These logs capture:

- Who was trained
- Who trained them
- What were they trained on
- When they were trained

Such logs may be kept with other entries in personnel training (CITI training, CVs, etc.) or may have their own location in the study binder. Check with your IRB, sponsor, or PI to see if and where these logs should be maintained.

References

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Section 2

THE RESEARCH QUESTION

The research question will dictate the entire course of study, including what population will be involved, what treatment or disease will be evaluated, and what study design will be implemented. Because the research question, including its very verbiage and formatting, entirely commands your investigation, its development will require serious thought. David L. Sackett of McMaster University's Department of Clinical Epidemiology & Biostatistics once purported that ""one-third of a trial's time between the germ of your idea and its publication in the New England Journal of Medicine should be spent fighting about the research question."[1]

What is a research question?

The research question, perhaps unsurprisingly, is what your research project seeks to answer. This represents a gap in current medical knowledge or a question yet unanswered in the literature. The answer to this question should be clinically useful and of interest to the public.

How do I come up a research idea?

The best research ideas are those that arise from daily practice. They may also come from your own perusal of the literature, either for your own interest or the benefit of a patient. It may come from your own interest, or maybe you left your PubMed tab with unanswered questions. "Research is too much work to not have a passion for what you are investigating."[2]

- You may see impressive treatment results in your own office and want to explore your own anecdotal evidence- is there something your colleagues should know for their own practice?

- You may wonder if technological advances or discoveries in other fields could be applied to your specialty.
- You may suspect a relationship between a frequently seen condition or disease and a specific medication, procedure, population, or a seemingly independent condition or disease.

How do I craft a research question to guide a project?

Research questions should be specific and of clinical relevance. Two acronyms are useful in the generation of research questions: **PICO(T)** and **FINER.**

PICO(T) is used to help formulate the question. It will eventually allude to your inclusion/exclusion criteria and other elements of your protocol.

Population (e.g. "post-menopausal women with dry eye disease")

- What group of patients are you interested in?
  - Those with a specific condition or disease
  - Those taking a certain medication
  - A certain demographic (age, gender, race, ethnicity, etc.)
  - A combination of the above
- What group of patients are you not interested in?
  - What

populations, demographics, medications, conditions, etc. may confound or adversely affect study results?

- This is important in developing exclusion criteria

- A specific, well-defined population will limit bias and aid in results analysis. It will also increase internal validity (whether observed results are due to the independent variable/intervention and not due to another source)
  - It may, however, decrease external validity (generalizability- can these results be applied to the population at large and not just this sample?)

Intervention (e.g. “omega-3 supplements”)

- Treatment, procedure, or process that will be applied to the population
- This will be your independent variable

Comparison (e.g. “placebo”or “artificial tears”)

- Control group
  - Is there a “gold standard” or current treatment that the intervention will be compared to?
  - Or will the intervention be compared

to placebo?

Outcome (e.g. patient-reported symptoms or clinical exam findings)

- How will you know if your intervention was significant?
- What will you measure in your two groups to determine which intervention was "best"?
    - This may be qualitative (e.g. "pain severity") or quantitative (e.g. "visual acuity")
    - Ideally, this will be a quantitative measure for statistical analysis
- This will be your dependent variable

Time (e.g. "one year"

- How long will data be collected?
- How long will patients receive treatment and/or be followed?[3,4]

FINER will help you fine tune elements of your question and project. It will also ensure that your research is meaningful, applicable, and worth the effort

Feasible- is this project doable? Is this project doable by you and your institution?

- How many subjects will you need? How hard is it to find patients who meet these criteria? How willing will patients be to participate?
- Do you, your research team, or your institution have the proper technical expertise to execute the project?

- Is the scope reasonable? How long will the project take? How much will it cost?

Interesting- will this project and its results grab the attention of your colleagues? Are you personally interested enough to see this through publication?

Novel- will this enhance medical knowledge? Will it build upon, confirm, or refute previous findings?

Ethical- will an IRB approve of this study? Is it safe and respectful of human subjects?

Relevant- is there a need for this information, either by patients, public health, or for future research?[5-7]

Now what?

With a working research question in hand, it is then time for a literature review.

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1. Riva JJ, Malik KMP, Burnie SJ, Endicott AR, Busse JW. What is your research question? An introduction to the PICOT format for clinicians. The Journal of the Canadian Chiropractic Association 2012;56:167-71.

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Section 3

CONDUCTING A LITERATURE REVIEW

A literature is a comprehensive assessment of existing medical and scientific literature relevant to your research question. This is first done to ensure that your topic has not already been adequately addressed in the literature. The current literature will then inform your work by detailing previous efforts, providing background and a rationale for your work, and may even suggest useful methodology. Moreover, a literature search will provide references for your IRB/FDA submission and eventual publication. Keep in mind that your research question may change and evolve throughout the review process.

Medical knowledge is now developing and expanding at an unprecedented rate. Its accession is now easier than ever due to its digitization with the advent of the internet, e-journals, and search engines. Because of medicine's shift towards electronic publication, investigators should be very familiar with online literature searches. However, not all publications are shared electronically and many paper entries have yet to be indexed, so it is also important to consider offline searches.

Levels of Evidence

Not all studies and publications are created equal. Different study designs provide levels of evidence, with some of higher caliber than others. This is crucial to keep in mind as your explore the literature because not all articles are scientifically convincing and statistically valid. This hierarchy of evidence, from least to most convincing, is as follows:

1. Editorial/Opinion pieces

2. Case Reports (descriptive piece on an occurrence in a single patient)

3. Case Series (several case reports detailing the same occurrence in several patients

4. Case-Control Studies (comparison of subjects with/without disease, looking for association between disease development and risk factors/exposure)

5. Cohort Studies (look for disease/condition development in exposure group vs. non-exposure group)

6. Randomized controlled trials (random treatment assignment to observe effect of treatment(s) on outcomes)

7. Systematic reviews and meta-analyses (exhaustive review of literature and RCTs related to a specific research question)

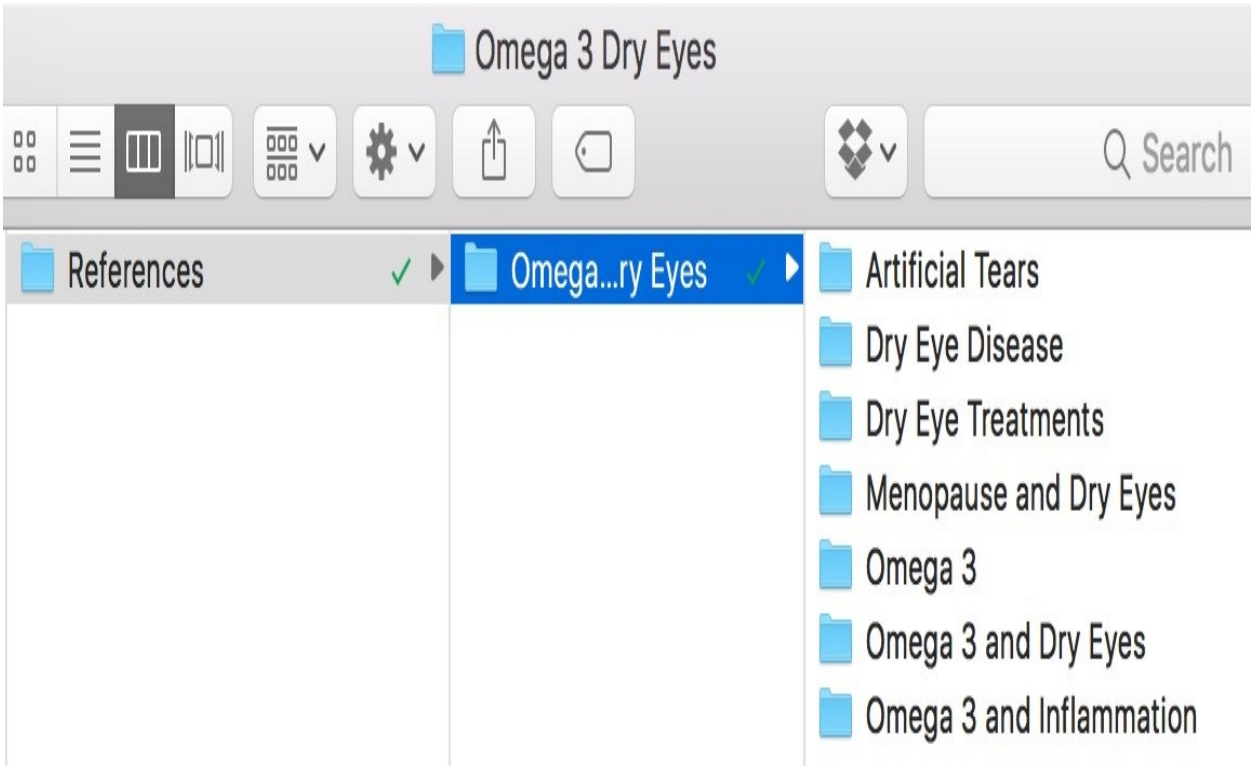
While RCTs are usually the "gold standard" for evidence-based medicine, they are often unethical or inappropriate for certain research questions. During your literature search, pay special attention to systematic reviews and meta-analyses: because they summarize the relevant literature to date, they have done much of the work for you and are often a treasure trove of helpful references.[1,2]

Citation Management

Storage

All relevant articles should be saved for future reference and citation in publications. These articles' own references may also be useful and point to papers that your initial literature search did not turn up. You should store all references and their citations in a well-labeled, searchable directory (which is either on a network drive or a hard disk that is backed up. Your project should have its own labeled folder with a "References" subfolder. This subfolder will then have several subfolders, each corresponding to relevant themes, terms, or

topics. Below is an sample from our dry eye example:



Citation Management Programs

Several programs citation management programs exist that will keep track of your references and aid in the citation process.[3] Many of these work with Microsoft Word and will keep track of your references as your write, which is essential when drafting publications. These include programs such as EndNote, Reference Manager, and Procite. Selection of a program comes down to personal choice and availability, with many institutions providing at least one of these programs. Check your institution's library website, or speak with a librarian to see which is provided free-of-charge (they are rather expensive if you have to pay for one yourself).

These programs are beautiful they often spare you the frustration of formatting citations. Alongside text or PDF versions of articles, online databases will often have downloadable citation files for each publication it has access to. This means that in addition to

providing the article itself, many websites will also provide a file for your citation manager that it will then store for you. Citation files are usually of .bib, .ris., or .txt formats. These files may easily be found on websites alongside their article (literally under "Citation") or may be under "Send to" (PubMed) or "Export" (ScienceDirect) menus.

Performing the Literature Search

Electronic databases are usually the best places to begin your searches because they offer simultaneous access to collections of journals, publications, and articles. When searching, keep the following in mind:

- Search terms related to all aspects of your research question
    - Individually search for articles related to your study population, disease/condition, and intervention (start broad)
    - Then, search for combinations to identify more directly relevant articles (e.g. study condition in that specific population)
- Review articles and meta-analyses will save you time by having already reviewed the literature (complete with references)
- Look for more recent articles by sorting by publication date (newer articles will cover older publications in introduction/discussion sections)
- Look for articles related to the ones you identify as being relevant to your project (either because they are linked or because the search engine deems them to be similar)
- Articles that are frequently referenced are usually important papers in their field

Using Electronic Databases

Electronic databases have made searching the literature incredibly easy. However, because of the huge volume of publications now at our disposal, smart, efficient searches are key.

PubMed (https://www.ncbi.nlm.nih.gov/pubmed/)

PubMed is a free search engine linked to the MEDLINE (Medical Literature Analysis and Retrieval System Online) bibliographic database provided by the US National Library of Medicine (NLM). It covers publications in the life and biomedical sciences, including medicine, nursing, dentistry, and public health. Advanced searches can be performed to specify a specific date range, journal, or author, and results can be sorted by similar characteristics. Each search result will have its own page with citation, with most articles having at least an abstract. PubMed will also provide you with links to articles similar to the one you are reading, as well as a list of articles that have cited it. At the top right, you will find links to the entire article if they are available to you (usually by institutional subscription). PubMed has at least 27.4 million records with some dating back to 1809 as of July 2017.[4]

https://www.nlm.nih.gov/services/pubmed.html.

Google Scholar (https://scholar.google.com/)

Google Scholar is able to search a wide range of publication in a variety of formats (including theses and patents), encompassing both digital and paper copies of articles. It is even able to locate the latter in libraries. Much like PubMed, only abstracts and citations are common, with many articles requiring a fee for their entirety. Google Scholar is unique in that it prioritizes search results by the author's impact, the journal's ranking, and how many other articles are linked to them.

In 2012, Nourbakhsh et. al compared medical literature searches when using PubMed and Google Scholar. They found that the two search engines usually produce different search results, with Google Scholar's being more relevant and potentially useful in initial

literature searches. There are certainly more search engines out there, but these two are among the most popular. Consider also browsing: Web of Science, Scopus, and Embase.[5]

Institutional Databases

Most institutional libraries offer online access to their collections, even boasting digital copies of printed publications. Check your institutional library's website or speak with a librarian to see what is available. Much like with PubMed, institutional subscriptions will provide you with direct links to articles.

Offline Literature Searches

While online literature searches are usually sufficient, they are by no means exhaustive. The following are also great starting points:

- Speaking with colleagues and mentors
- Local and institutional libraries
- Trained science and medical librarians (if available at your institution)
- Print publications (your institution and its departments will likely subscribe to JAMA and speciality journals)

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Section 4

CHOOSING A STUDY DESIGN

The nature and format of your research question will dictate the most appropriate study design. Clinical research studies are usually divided into observational (association or relation) and interventional (causation) projects, each with its own subsets of study designs. Before initially evaluating design options, it is helpful to develop your project's aims and hypothesis to better specify which design will be most appropriate. IRBs, the FDA, and grant committees will also judge your proposed project by its anticipated ability to answer your question and complete your aims.

Hypothesis: essentially what you believe your project's results will show based on your review of the literature

- For our dry eye example, "Omega-3 supplementation in post-menopausal women with dry eye disease will improve signs and symptoms of dry eye disease when compared to artificial tear usage alone."

- Note: Ethically, interventional studies are only justified if the scientific and medical communities are in a state of clinical equipoise. That is, it is only ethical to subject human subjects to the burdens and risks of research if there is an "honest and professional disagreement among expert clinicians about the preferred treatment."[1,2]

Aims: a statement of the goals you hope to accomplish with your research project

- For our dry eye example, "In this study, we seek to evaluate whether or not omega-3 supplementation will improve dry eye signs and symptoms of post-menopausal

women with dry eye disease."[3]

Research Question to Clinical Research Design

Research questions can be broken down into three categories:

1. Descriptive: describes an occurrence

- Spectrum or frequency of disease or characteristic

2. Relational: describes a theoretical relationship between two occurrences

- Associations between risk factors and diseases or conditions by comparing two groups

3. Causal: describes a theoretical change in an outcome because of an intervention

- Use of a therapy or agent to modify an outcome or disease process[3-5]

The first two types of questions are best answered by observational studies. These can be retrospective (the outcome of interest has already occurred, and the data already exists, such as in medical records) or prospective (the outcome of interest has not yet happened, and the data has yet to be collected). Note: prospective studies are preferred when possible; retrospective studies rely on data that already exists and was not collected under a protocol, so information may be incomplete or not properly formatted for a study (i.e. trying to repurpose medical records collected by a variety of care providers as study data).

To look at the frequency of a condition or characteristic with an observational study:

Cross-sectional Study ("snapshot" of baseline characteristics)

- Determines prevalence, or what proportion of a

population has a specific disease, condition, or characteristic at a point in time
    - Can also collect data on variables associated with that condition and population

- Can look at an outcome (e.g. diabetes) and a variable (e.g. number of meals at fast food restaurant)

- Best done with surveys (though subject to recall bias)
    - Avoid losing patients to follow-up (one-time data collection)

- Usually inexpensive and quick[4,5]

Cohort Study (following two groups, one with risk factor and one without, to look for development of specific outcome)

- Describes incidence and associations between diseases and risk factors

- Cannot prove causation, only indicate association

- May be difficult with rare diseases

- Can be retrospective or prospective (more common)
    - Retrospective: look at medical records, identify two groups separated by a risk factor, look for incidence of desired outcome

    - Prospective: identify two

groups separated by a risk factor and look at respective incidences of desired outcome

- Better than retrosp

  design; data is collecte under a protoco and less subject to interpr

- Can be used to track

progno after exposu

- Takes longer than a retrosp

design and is more expens

Case-control (match patients with identical, important variables who are separated by having a disease or condition)

- "Case" = those with the disease or condition; "Control" = those without
- Useful for rare diseases
- Can examine what factors may be of interest or related to the disease/condition
- Variables may be open to interpretation (data already exists and was not collected under a protocol)[4,5]

Randomized controlled trial (RCT) (manipulate variable by providing intervention to observe effect on specified outcome)

- Therapeutic or preventative study
    - Provide one group with experimental treatment, while other group receives placebo or standard therapy
    - Can help establish causation between an intervention (agent, therapy, procedure, treatment, etc.) and a specific outcome
        - Control for variables that may skew results (confounding factor) so that observed changes in outcome are likely due to treatment
        - Subjects are randomly assigned to treatment vs. non-treatment group so that potentially confounding factors are equally distributed
        - May be single-blinded (subject-level) or double-blinded (subject- and investigator-level) to control for bias
        - Expensive and time consuming
        - Ethical considerations

(is it appropriate to withhold treatment?)

- Use placebo as control if no standard treatment exists
- Use standard treatment as control if one exists[4-6]

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Section 5

WRITING THE RESEARCH PROTOCOL

The research protocol is the core document of any clinical research project. This one document reviews the existing literature, identifies a gap in medical knowledge, and details exactly how that question will be answered with a systematic course of study. The protocol, or research plan, is also the main document that regulatory authorities (primarily IRBs) will review to ascertain whether or not your project is scientifically and ethically sound enough to warrant the inclusion of human subjects. Because of its weight, it is important that the research protocol is as complete, logical, and clear as possible. Though protocol formats vary between institutions, all will include the following sections and elements:

Project Title

Specific Aims/Objectives

Background and Significance

Research Setting and Personnel

Experimental Design and Methods

- Drugs, Devices, and Biologics
- Recruitment Methods
- Inclusion and Exclusion Criteria
- Number of Subjects
- Study Timelines

- Study Endpoints/Outcome Measures
- Procedures

Data Management, Confidentiality, and Analysis Plan

Potential Risks and Benefits

Safety Reporting and Monitoring

Subject Reimbursement/Compensation

Additional Forms: Consent, Recruitment Materials, Case Report Forms, etc.[1]

A note on industry-sponsored studies and multicenter RCTs

In the event that your institution is acting as a study site for a mulitcenter trial, whether industry-sponsored or otherwise, the sponsor will provide the study protocol to all sites in the same format. It is thus the responsibility of the study site to convert this universal protocol into an institution-specific protocol. This involves using the provided protocol to complete your own IRB's study documents. Sponsors should provide enough information to do this, but this process may require additional communication between IRB, site, and sponsor in order to complete the requisite forms to receive IRB approval. Sponsors may also request to see draft protocols before submission.

Project Title

The full project title should be 12-15 words max and convey a general idea of your research plan, including what, who, where, and when.

"The Effects of Omega-3 Supplementation in Subjects with Dry Eye Disease"

Aims/Objectives

This section is literally what you intend to do with your project.

This should include a simple, clear explanation of your study's objectives and what hypothesis will be tested. Essentially, you are detailing how you will answer your research question. Your entire protocol should convince a reader that these aims are specific, realistic, and achievable. This section should be a few sentences at most (consider this an introduction).[2]

Background and Significance

This is where you walk the reader through your literature review. You should detail the condition or disease you are interested in, the current work in the field done up until now, and identify the knowledge gap that you intend to fill. This section should essentially "hold the hand" of the reader so that they too logically conclude with your aims and objectives. Remember to address the following:

- How this project will build upon prior work
- Limitations of previous studies
- The need for this research to occur
- How this research will benefit both patients and the scientific community
- Most recent publications in the field

This section will also be useful in the future; it contains your entire literature review in one convenient place and can be recycled for the introduction and discussion sections of future publications.[1,3]

<u>Research Setting and Personnel</u>

Use this section to indicate what facilities and services will be utilized throughout research conduct. This should include what hospitals and clinics subjects will be seen at, what departments will be involved, and what laboratories will provide study services. This should also identify the individuals working on the project, their roles (investigator, coordinator, safety monitor, etc.), and documented qualifications (CVs, medical licenses, CITI training, etc.) You may want to discuss who will be blinded/unblinded, who will be collecting

the data, and who will have access to confidential patient information.

Experimental Design and Methods

This section is the bread and butter of your protocol. It should indicate what kind of study will be performed, how subjects will be identified (recruitment methods), who will and will not be enrolled (inclusion/exclusion criteria), and what outcomes will be assessed to determine whether or not the research question was answered (endpoints/outcome measures).

a. Drugs, Devices, and Biologics

If your study is interventional, in that it is evaluating the effects of a new drug or procedure, describe the experimental treatment. If using a drug or device, reference the IND/IDE number and indicate the status of that application with the FDA.

Be sure to include: dose, route of administration, experience with previous use, and any existing safety and efficacy data, either from the literature or from previous studies. Note the phase of testing (if a drug) and any significant/nonsignificant risks.

b. Recruitment Methods

How will subjects be found for your study? List every method that you will utilize (See **"Recruitment"** section). Include any recruitment materials that require approval with your initial submission to the IRB. Note that proper informed consent will be obtained from every subject before beginning research activities.

c. Inclusion and Exclusion Criteria

Detail the combination of biomedical and behavioral characteristics of subjects that will be included in your study, as well as those of subjects who will not be included. Criteria should be indicative of your target population (to ensure

generalizability) and should also control for confounding factors. For instance, you may want to exclude subjects who are taking another medication for your condition of interest (if ethical)- how would you otherwise discern if any observed effects are from the study drug or the drug that they are already on? All criteria, especially those including vulnerable populations, must be justifiable.

Common Inclusion Criteria:

1. Sign and date the informed consent form approved by the IRB
2. ≥ 18 years of age
3. Women of child-bearing potential must agree to use a reliable method of contraception during study participation and must demonstrate a negative urine pregnancy test at the first study visit
4. Be willing/able to return for all study visits and to follow instructions from the study investigator and his/her staff

Common Exclusion Criteria

1. Allergic, by patient report, to ingredients of the active or placebo pills
2. Pregnant or nursing/lactating
3. Participation in a study of an investigational drug or device within the 30 days preceding the first study visit
4. Cognitive or psychiatric deficit that

precludes informed consent or ability to perform requirements of the investigation.

d. Number of Subjects

Indicate the number of subjects that will be recruited for your study. This should be supported by sample size and power calculations to demonstrate the ability of your study design to detect statistical significance, if it exists. These calculations can be difficult, so it is recommended that you work with your institution's biostatistics core or consult someone with a sufficient knowledge of statistics.

Values needed for these calculations, such as *means*, *variances*, and *effect sizes* are typically derived from the literature review and reflect values associated with your primary outcome (see **Study Endpoints/Outcome Measures).**

Some notes on these calculations:

- Power is typically set to 80% (the larger the power
- Statistical significance (alpha) is typically set to 5% (0.05)
- Many articles and calculators exist online to aid with these calculations:
    - https://www.ncbi.nlm.nih.
    - https://www.ncbi.nlm.nih.
    - https://www.uv.es/uvetica
- Indicate what statistical tests and what programs (and version numbers/year) were

used in calculating your sample size

It is unethical to enroll subjects if these calculations have been done improperly; there must be sufficient evidence to support the indicated enrollment size in order to justify human participation. It is also unethical to enroll more subjects than is absolutely necessary to answer the research question.[4-6]

e. Study Timeline

Detail your study's phases and stages, pairing each with an anticipated duration. This should include time for recruitment, follow-up, analysis, and publication. Example:

- Recruitment (3 months)
- Follow-up visits (12 months)
- Data analysis (2 months)
- Manuscript development and submission (2 months)

f. Study Endpoints/Outcome Measures

Study endpoints and outcomes are the variables that your study is looking for a change in. Clinical research projects need at least a primary outcome measure, which is the variable you will track and use to determine whether or not your research question has been answered. Sample size and power calculations should be based around your primary outcome. Endpoints are commonly evaluated by looking at the mean change in the variable from the beginning of the study (baseline) to the end of the study. They may be:

- Subjective, or patient-reported (e.g. pain)

- Objective, or change in the number of events (e.g. deaths, as in a change in survival),
- Something that can be measured physiologically (e.g. change in lipid profile)

Especially in interventional trials, IRBs may want you to indicate that these variables and data analyses will occur throughout the trial, not just as the end. This is done ethically so that trials are stopped when interventions are found to be harmful or when they are found to be extremely beneficial (in which clinical equipoise is disturbed).[1]

g. Procedures

What procedures will subjects undergo? How many times will subjects come in for the study (how many study visits are there)? This section should include a description for every research activity that you expect subjects to participate in. This may include:

- Collection of demographic information
- Surveys and questionnaires
- Clinical examinations and measurements
- Surgical procedures
- Treatment or intervention (e.g. study drug usage)

Please note that IRBs may request to see any forms that subjects will fill out, include surveys, questionnaires, and CRFs. You *must* indicate which activities are a part of standard, clinical care and which are specifically research

activities. In addition, each description should include:

- When and how often each activity will occur (every visit? once?)
- How long each will take
- Who on the research team will do what
- What instructions will be given to subjects

If your project involves more than one study visit for subjects, you may want to include a visual schedule of procedures:[7]

		Visit (Month)				
Procedure	-2 wks SV	**00**	**03**	**06**	**09**	**12**
Obtain Informed Consent	X					
NAME OF Questionnaire	X	X	X	X		X
Health Economics Questionnaires (SF-36, WPAI, Healthcare Use)		X		X		X
Medical History and Events	X	X	X	X		X
Concomitant Medication Query		X	X	X		X
Adverse Event Query		X	X	X		X
STUDY-SPECIFIC TEST 1	X		X			
STUDY-SPECIFIC TEST 2		X		X		X
Blood Collection		X				X
Collection of Unused Study Drug		X	X	X		X
Randomization		X				
Dispense Study Drug	X					
Reminder Calls (2 weeks before each visit)		X	X	X		X
"Check-In" Telephone Call					X	X
Letter to Encourage Compliance (sent 1 month after each visit)		X	X	X		

Data Management, Confidentiality, and Analysis Plan

Data Management

Describe what data will be collected and how it will be stored.

- Will data be collected on paper? Where will paper copies be stored?
    - Subject binders?
    - Will these be under lock and key?

    - Who will have access?

- Will paper data be transferred to an electronic database (data entry)? Is the hard drive HIPAA-compliant and encrypted? Who will have access?
    - How often will data entry occur? Who will do this?

- What software will be used?

- Will data be backed up?

- How will data be disposed of?

Confidentiality

- Will data be de-identified (e.g. will subject IDs be used in place of identifiers)?
    - Will identifiers (names, birthdates, SSNs, etc.) be collected?

    - Where will information linking individual subject identities to subject IDs be kept?

    - Who will have access?

- Are there situations in which privacy and/or confidentiality will be broken?
    - Such as in a medical emergency

Analysis Plan

- Describe the data being collected
    - Name variables

    - Describe methods for quantifying clinical observations

- Indicate *specifically* how data will be used to answer the research question:
    - Type of statistical analysis software used
    - Outcomes and effect measures (with confidence intervals)
    - Which statistical tests will be used
    - Type of sample (paired vs. unpaired)
    - Distribution assumption (normal vs. abnormal)
    - Modeling methods
- Indicate whether every subject randomized will be included (intention to treat - ITT) or if only those who are compliant and complete the study (per protocol - PP)
    - Include justification
- Note procedures for interim analysis
    - Are there any "Stopping Rules"? (e.g. subjects are harmed by study, or intervention is found to be beneficial early- clinical equipoise disturbed)
- How will missing or incomplete data be handled?[2,4,8]

Potential Risks and Benefits

Benefits

- Describe any potential benefits for research subjects. Indicate their magnitude, probability, and duration
- These may include: treatment, additional information about their condition, counseling, etc.

- *Compensation is not considered to be a benefit.*
- If there are no anticipated benefits, indicate this and instead note anticipated benefits for the advancement of medical and scientific knowledge. You may want to add that there may be anticipated benefits for future patients with their condition.

Risks

- Describe any potential or anticipated risks to research subjects. These may be medical, psychological, social, economic, or legal.
- These may be immediate or long-term, and may include discomforts and inconveniences.
- Indicate their magnitude, probability, and duration.
- Note precautions taken to minimize or eliminate these risks.
- Describe the support available (medical, psychological, social, etc.) that are available for subjects throughout the study for research-related risks.
- Justify why these risks are necessary to complete the study. This may tie back into benefits for general medical knowledge and treatment.

<u>Safety Reporting and Monitoring</u>

- Note that all medical and unexpected events will be reported per local institutional and IRB guidelines (and FDA guidelines, if applicable).
    - Adverse events: any negative medical development occurring during the study period, whether conceivably related to the study or not
        - Subjects should be encouraged to

report these at study visits or by telephone

- Adverse event logs should be included in subject binders/charts

- Serious adverse events: fatal, life-threatening, requiring inpatient hospital stay, resulting in significant disability or inability to conduct normal life functions, congenital anomaly or birth defect in child born to mother exposed to study drug or procedure
  - IRBs usually require that these be reported within 24 hours
  - SAEs should also be entered into a subject's AE log

- Indicate how subject's safety will be ensured and monitored.
  - This usually involves appointing a clinician (perhaps on the research team) who will serve as a medical monitor. This individual will review all AEs and SAEs and will determine if they are related to the study intervention or protocol. In extreme circumstances, the safety monitor may recommend that the study be terminated to protect subjects, especially if causality is determined to be related to the study.
  - If this is a large, multicenter study, an independent data safety monitoring board

(DSMB) may be appointed. This is a diverse team of professionals related to the study (e.g. other specialists, clinicians, psychologists, nutritionists) whose expertise will be useful in evaluating subject safety concerns. This team will evaluate AEs and SAEs at prespecified intervals.[7]

Subject Reimbursement/Compensation

Detail if subjects will be reimbursed or compensated for their participation in the study, either financially or by other means. IRBs will evaluate this to make sure that payments are not so large as to be coercive, but are not too small such that they are inappropriate for the burdens of participating. This information should also be covered in the consent.

> **Reimbursement** covers travel for study purposes, lost wages for participation, parking costs, etc. This essentially makes up for any incurred costs relating to study participation.
>
> **Compensation** is given for subjects' time and effort.

You should also note how subjects will be reimbursed or compensated if they exit or withdraw from the study early. Payments should be prorated, and subjects cannot be punished for early exit.[7]

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7. Bankert EA, Amdur RJ, Amdur RJ. Institutional review board : management and function. 2nd ed. Sudbury, Mass.: Jones and Bartlett; 2006.

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Section 6

WRITING THE INFORMED CONSENT OR WAIVER

If your study requires the consent of human subjects, it is usually most convenient to draft the informed consent document after writing the protocol because the two share some common elements. The important difference, however, is audience. While the protocol is written for the investigative team for the purpose of carrying out a study, the informed consent is aimed at individuals who are considering participation. Therefore, the consent document focuses primarily on what participation entails and is written so that *anyone* can understand it, not just the medically and scientifically trained.

Most IRBs will have consent templates and checklists available online. Use these and portions of your protocol to draft your consent, but be careful to adjust its wording to suit a broader audience. Most consent documents include a HIPAA authorization section. If your study involves a pediatric population, consent will be obtained from the child's parent or guardian. Your IRB may require that you also obtain the child's assent (your IRB may have a separate consent template for pediatric studies).

There are also certain circumstances and study designs which preclude usage of informed consent. In this situation, such as when performing a chart review, waivers for obtaining informed consent are available (see below).

Informed Consent

Required Elements

- *All must be in lay language! (6th-8th grade reading level; use 2nd person)*
- Nature and purpose of the study
- Indication of the study's sponsor
- A statement that this study involves research (so not to be confused with care)
- Reason why this potential subject is being asked to participate
- Study design
- Expected duration of study
    - Number of expected subjects
    - Number of study groups
    - Use of randomization
    - Use of placebo (describe as an "inactive substance" that looks just like the study drug)

    - Number of visits (may want to present visits and relevant procedures in a table; see the procedure table in “Writing the Research Protocol”)
- Study procedures and treatments (description of device, if applicable)
    - Where these will take place
    - If collecting blood, indicate how often and how much (use tablespoons or teaspoons as a measure, not ml)
- Compensation or reimbursement
- Potential risks/discomforts for the subject

- If study is greater than minimal risk, indicate compensation in case of injury

- Potential benefits, either directly to the subject or to society
- Available alternatives to participating, if any
- An indication that participation is voluntary and that subject may withdraw at any time without penalty
- Additional costs related to participation (who will pay for what)
- How confidentiality will be protected and who will have access to the data[1]

Informed Consent Waivers

In the event that informed consent cannot be obtained, either because it is not feasible per the study design or in an emergency situation, you may apply for a waiver of consent. IRBs typically provide instructions and templates for when this is applicable. While IRBs will grant waivers on a case-by-case basis, there are 3 common study designs or circumstances for which this is common:

- **Retrospective Chart Reviews**

  Data has already been collected and will be de-identified for use in the project. Therefore, the consent document would be the only record linking subjects to the study and thus represents a potential risk. Also, because of the sheer volume of subjects that may be included, this could otherwise require contacting and obtaining consent from hundreds of past patients.

- **Emergency Medicine Research**

  In studies related to emergency situations, it is often not possible to obtain informed consent before an investigational drug or treatment is administered due to the study population's medical condition. For instance, the population being studied may be unconscious or comatose, and it would be unethical to withhold treatment until consent is obtained. This is especially true in instances of life-threatening conditions. In the event that subjects improve or recover from their condition after treatment, informed consent should *then* be obtained.

- **Pediatric Studies: Parental/Guardian Permission is Not Protective**

  In studies of certain pediatric populations, such as abused or neglected treatment, it may be unethical to obtain permission from parents or guardians either because of unavailability or because their expressed consent does not indicate sufficient protection of the child's rights and welfare.[1]

References

1. Bankert EA, Amdur RJ, Amdur RJ. Institutional review board : management and function. 2nd ed. Sudbury, Mass.: Jones and Bartlett; 2006.

Chapter 6

RESEARCH COMPLIANCE AND AUDITING

Sections

Section 1

THE REGULATORY BINDER AND ESSENTIAL DOCUMENTS

Any research project involving human subjects must maintain a **regulatory binder**. This binder contains all documents and paperwork necessary for the conduct of the trial.[1] It must be organized and contain certain elements so that it can be inspected or audited by study staff, IRB, or other regulatory agencies at any time.[2,3] **This binder represents your entire study! Documentation is incredibly important in clinical research**. If something was not documented and accounted for, it did not happen. The binder should also serve as a complete record; a stranger should be able to read the binder and learn everything about the trial and what has happened. It should stand on its own and not require a member of the study team as a guide or to fill in any gaps.

Essential documents are of specific importance. These documents permit conduct of the trial and serve to demonstrate compliance with Good Clinical Practice (GCP), research ethics, and regulatory bodies (IRB, FDA, etc.).[2] They also speak to the integrity of the study team and its data. These include but are not limited to:

Signed protocol and amendments (demonstrating that the staff has read and understands the protocol)

Current, IRB-approved consent form (to indicate information given to study subjects)

IRB-approved advertisements for study recruitment

Submissions, approvals, and all communication with the IRB (to demonstrate compliance)

Documentation of proper training and qualifications of all study staff members

Documentation of investigational product handling (certificates of analysis, shipping/storage/dispensation/destruction records)

Master subject list

Monitoring/auditing reports[3].

All IRBs will have their own requirements and suggestions for regulatory binder formats, so please check with your local institution for guidance. Below is a suggested structure. Because this is a template, feel free to omit certain sections if they are not applicable for your project.

Regulatory Binder

The binder should kept up to date with new documents added ASAP. **File in reverse chronological order in each section**. For instance, the latest IRB communication should come before older entries. Use labeled binder tabs for easy navigation (use labels for sections under **Contents** below). Certain sections may become so large that they are deserving of their own binder (this is common with IRB-related materials). If this occurs, label the new binder according to the study and also indicate what specific information it contains (e.g. "IRB Binder"). Place a "**note to file"** (see below) in the original location (the corresponding section) in the IRB binder indicating that its material has been moved to the new binder.

Location and Storage

The binder should be stored in a safe, secure location where it can be easily found by the study team. You may want to identify a specific member of the study team to maintain the binder and

documentation.

Cover/Outside

The binder should be labeled so that it is easily identified and associated with a particular study. Labels can be made in Word (and inserted into transparent cover sleeves) or on a label maker. Both the cover and the spine should have:

- IRB-assigned study number
- Study Title
- PI
- Sponsor (if applicable)
- Institution

Note: you may one day have so many documents that you need several regulatory binders. Label all binders with their entry number (e.g. the first binder is binder 1 of 3, the second is 2 of 3, etc.)

Contents

Study contact information: 24-hour contact information for PI (and, if applicable sponsor and monitor)

- Address, phone number, fax, email, and beeper for each

Protocol: all versions of the study protocol in reverse chronological order

- Should include page where PI/study team has signed and dated to show that each version of the protocol has been reviewed

Investigator Brochure

- All information provided to study team regarding investigational drug (note: if

investigating a device, this may be a manual instead)

Study Staff

- Delegation log indicating roles/responsibilities of all study members
- Training documentation (CVs, CITI training, licenses, training logs, etc.) for all study members

Informed Consent/HIPAA Authorizations

- All versions of IRB-approved consent/assent forms in reverse chronological order
- May also include all IRB-approved recruitment materials (flyers, brochures, advertisements, etc.)

IRB Approvals

- All communications of approval from the IRB in reverse chronological order (all approvals, including those for initiation, renewal, termination, modifications, and additions)

IRB Submissions and Communications

- Copies of anything *sent* to the IRB (this includes all materials needing to be approved, notifications of deviations/adverse events, etc.)

Correspondence

- Any communications besides those with the IRB. This may be with the study sponsor, a monitor, etc.

Site Logs

- Screening/Enrollment logs (this may be kept in its own binder)
- Drug logs (to document receipt, storage, dispensing to subjects, return from subjects, or destruction)
- Refrigerator logs (to document daily temperature, if needed)
- Monitoring logs (to document frequency)

Laboratory Documentation (if study is using lab)

- Reference ranges for lab values
- Certifications for the lab (training documentation for lab director, lab accreditation, inspection records, etc.)

Notes to File

- Team-generated notes (often handwritten) used to document missing or incorrect forms
- May also indicate location of documents (e.g. may place a note to file in the IRB sections to indicate that they have been given their own binder)
- May also be used to document events, protocol deviations, or investigator/site-specific practices
- These are signed and dated by the author

Investigator-initiated studies: FDA Materials

- Only applicable if the study is under FDA jurisdiction and/or if the PI holds an IND for

the study

- This section may be given its own binder due to volume
- Includes all signed and dated submissions, approvals, and correspondence with the FDA:
  - FDA 1571 forms, FDA 1572 forms, reports, amendments, etc[4]

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Section 2

RECRUITMENT

Recruitment is an incredibly important part of the clinical research process; only successful, adequate recruitment will statistically power a study in order to answer its posed research question. Recruitment may be difficult, potentially to the rarity of the condition in question, local availability of eligible and willing subjects, or improper allocation of resources. As of 2001, it was found that 45% of all study delays are related to recruitment, with delays often exceeding 6 months. Investigators and sponsors may then incur extra costs in order to meet recruitment goals or may even expand their study's eligibility criteria, which risks reduction in study validity. It is therefore imperative that research teams develop a robust, flexible recruitment plan before enrollment begins to ensure that recruitment is as efficient and as effective as possible.[1]

Successful recruitment includes:

A pool of subjects that is representative of the study population in question

- Age, ethnicity, race
- Cultural diversity is strongly encouraged

Large enough subject pool to properly power the study

- Must meet minimum recruitment goals set out in protocol
- Need to realistically estimate number of potentially eligible candidates
- May want to consider over-enrolling to compensate

for drop-outs or incomplete data

Safe, secure, and confidential use of PHI

An efficient identification and screening process

- Want to have a high enroll/screen rate
- Need recruitment materials/activities to directly access only eligible subjects (want to spend as little time on ineligible subjects as possible)
- Need to consider inclusion/exclusion criteria

Recruitment of eligible and compliant subjects

- Need to ensure that subjects will complete the entire duration of study (subjects dropping out early represent wasted time and effort)
- Compliance is heavily related to rapport between subject and investigative team
- Compliance is also related to barriers to participation (may want to compensate subjects for their time or travel needs)
- May need to use personal judgment in evaluating whether or not a potential subject will be compliant

The use of several diverse and effective recruitment tools

- Fliers, phone calls, advertisements, conversations, etc.

Sufficient personnel and resources

- Need to consider costs in advance (e.g. for personnel time, subject reimbursement,

printing/advertisements costs, etc.)

- Should respond to interested subjects ASAP (e.g. return voicemails on same day or next morning)
- Schedule subjects for screening ASAP after contact (don't make subjects wait a week after talking to you- schedules and interests may change quickly![2,3]

Planning Recruitment

The following should be considered when developing a recruitment plan:

IRB requirements

Is consent required or is the study exempt? Will the team apply for a consent waiver?

What recruitment materials (fliers, phone scripts, ads, etc.) need to be reviewed by the IRB?

Study timeline

Are there recruitment deadlines? How much funding is available?

Consider how long a subject will be followed (i.e. if each subject is followed for a year and you enroll your last subject in June, a completed data set will not be available until roughly June of the following year)

Inclusion/Exclusion criteria

How easy is it to qualify for the study? Investigators may want to browse their own patient databases to estimate this. Can subjects be easily recruited from the investigator's own patient pool or colleagues' patient pools?

Are many people taking a medication that may exclude them from the study?

Will eligibility be confirmed at the first visit, or will basic elements of eligibility be confirmed over the phone?

- The latter saves time in that obviously eligible patients will be screened out over the phone, saving them time by not having to come in. This requires additional IRB review (see below)

Study protocol

How many people must be enrolled at minimum? How many can be enrolled at maximum?

How many subjects should be enrolled per week/month to meet deadlines?

What risks/benefits will be most important to potential subjects in making their decision whether or not to participate?

What does participating entail? What do you want to highlight for a subject over the phone vs. in-person? (e.g. how many visits, how long each visit is, randomization, etc.)

Personnel considerations

How much time per day can be devoted to recruitment activities?

Who will answer phones, respond to voicemails, and return emails?

Subjects should always be contacted by someone they already know if possible (this is usually the investigator or physician if the potential subject is one of their patients)

Associated costs

Time/effort for personnel

Cost for printing ads, brochures, fliers, online advertisements, etc.

Compensation/reimbursement for subjects to travel/participate

IRB Requirements

IRBs will be interested in reviewing recruitment procedures and materials because recruitment is inherently tied to consent; it is essentially the beginning of the consent process. For instance, IRBs must ensure that subjects are treated ethically and are not coerced during recruitment procedures. Therefore, IRBs will need to review and approve of all recruitment-related plans and materials.

IRB requirements vary between recruitment methods, with some requiring only mention in the study protocol while others may require a physical IRB approval stamp. Some studies may also qualify for waiver of the consent process, or exemption from IRB review altogether. IRBs will also be interested in confidentiality procedures, such as what the study team will do with the identifying information for individuals who chose not to enroll or who drop out from the study.

All recruitment activities must be mentioned and justified in the study protocol. Certain procedures will then require additional IRB review.[3]

Recruitment activities not requiring explicit IRB review (must only be mentioned in IRB protocol; no additional paperwork required)

Investigator approaching own patients (need to consider potential for coercion due to dependent relationship)

Word-of-mouth (any written materials may require IRB approval)

Recruitment activities generally requiring explicit IRB review and approval (must be mentioned in IRB protocol *and* any written material must be individually reviewed/approved)

Sending letters to colleagues/physicians asking for referrals of potentially eligible patients

Sending letters to an investigator's own potentially eligible patients

Fliers

Advertisements (radio, newspaper, internet, television, etc.)

Phone scripts for introducing the study/determining eligibility by phone

Use of a database of potential research subjects (database must have been previously and separately IRB-approved; subjects previous indicated and consented to being contacted about potential research opportunities)

Recruitment activities which may be eligible for Waiver of Consent/HIPAA Authorization (must be justified in protocol and may require a Waiver Request form)

Chart review to identify potentially eligible subjects who will then be contacted regarding participation

- Must justify why study cannot be done without a waiver in protocol
- Must still collect informed consent prior to enrollment
- Recommended that potentially eligible subjects are contacted by someone they are already familiar with (e.g. clinician or nurse already involved in their care)

Chart review studies in which subjects will not be contacted

- Must justify why study cannot be done without a waiver in protocol[4,5]

RECRUITMENT METHODS

Below are activity-specific details for different recruitment techniques, including what an IRB will typically require, what should be mentioned in the study protocol, and templates for different forms.

Approaching an Investigator's Own Subjects: in-person

Description: Approaching a potentially eligible patient in clinic/hospital (e.g. subject is present for an appointment, procedure, etc.)

IRB Review: Must be mentioned specifically in recruitment section of study protocol (no additional review).

Template: "Subjects may include previously diagnosed (name condition) patients of the principal investigator. The principal investigator may approach potential subjects during routine appointments regarding possible participation int he study. Once the patient has been told about the study, the PI will ask if they are interested in participating. If the patient indicates they might be interested, the study coordinator or PI will speak with them to establish a separate visit to return for study participation. If they wish, the patient can take a blank copy of the consent form home to read. The investigative team will be clear when speaking to patients about possible study participation that their decision to participate or not will in no way affect their routine care at (institution)."

Approaching an Investigator's Own Subjects: by mail (recruitment letter)

Description: Sending letters detailing the study to the investigator's established patients, including contact information if patients are interested in participating or have questions.

IRB Review: Must be mentioned specifically in recruitment section of study protocol. Letter template must be approved by the IRB. Remember to send to your IRB in a format that can be edited (e.g. Word, not PDF) in case edits need to be made.

Contents: Should include:

Name of PI

How the patient's information was obtained

Description of study, procedures, and time commitments (how many visits, how long each visit is, etc.)

Contact information for questions/participation

Notice that participation is voluntary

Departmental letterhead

Signature of someone involved in patient's care

Template:

a) in study protocol:

"The PI may also recruit his/her previously diagnosed (name of condition) patients by mail. In this event, letters will be submitted for IRB approval before use."

b) letter template:

Date

Patient's Name

Address

Re: (Condition) Research Study

Dear _____,

Dr. _____ at (name of institution) is currently studying (condition, "a new medication" for condition, "a new treatment" for condition, etc.) A review of your medical record indicates that you may be

eligible to participate for this study if you are interested. The study involves being randomly assigned to one of two treatments, one of which is experimental while the other is placebo/current medication/coming to (institution) once a week for blood draws/etc. Study participation will involve at least X number of visits over X time (days/weeks/months).

If you may be interested in participating in this study or have any questions, please call Dr. _____ or the study coordinator _____ at (phone number) or (email address). You will not be contacted about this study unless you contact us first.

Participation in research is voluntary. It will not affect your treatment at (institution) if you decide not to contact us about the study or decide not to participate.

Sincerely,

(name and signature of treating physician)

Approaching Subjects by Phone

Description: Either:

Responding to a phone call from someone interested in participating. Investigators may send letters introducing the study to their patients, inviting them to participate, or potential subjects may call in reference to a flier, advertisements, etc.

Calling potentially eligible subjects who are established patients or from a research database (note: call must come from someone who has legitimate access to their information, either by being a member of their care team or someone with IRB-approved database/record access)

Phone calls are then used to answer any questions, briefly describe

the study, determine basic eligibility, and schedule an in-person interview to obtain informed consent and verify complete eligibility.

NOTE: "Cold calling" is prohibited. This is when an investigator contacts a potential subject knowing that this individual may be eligible, but the investigator is unknown to the subject (e.g. the investigator has never met the subject and is not involved in their care).

IRB Review: Must be mentioned specifically in recruitment section of study protocol. Phone script must be approved by the IRB. Remember to send to your IRB in a format that can be edited (e.g. Word, not PDF) in case edits need to be made.

Contents:

a) in study protocol:

How screening will be conducted (responding to calls from subjects who saw ads, calling subjects to whom letters had been sent, etc.)

Who on the investigative team will be calling

Protections for privacy and confidentiality of screening information (Is the information stored? Where? Is it secure? What happens if the subject does not participate- is the information retained?)

- Retaining screening data is not encouraged; requires specific IRB approval and permission

Indication that oral consent will be obtained before obtaining identifiable/sensitive information

- NOTE: Your IRB may require a Waiver of Written Documentation Request to waive written consent before obtaining this information by phone - written informed consent will be required when the subject comes in.

b) telephone script:

if eligibility information will not be obtained by phone, at least:

- Introduction including who is calling and from what institution
- Invitation to participate in study and why (e.g. review of medical records notes that they have X condition, or they had Y surgery for Z condition, etc.)
- Brief description of study (purpose) and what participation involves (number of visits, duration of visits, responsibilities of subjects)
- A statement that participation is voluntary
- Time for any and all questions the individual may have
- A statement asking if the subject is interested in proceeding, which may include scheduling a visit, going through the oral consent process, answering eligibility questions, etc.
- A plan if the subject does not answer the phone
  - Leave a voicemail (must include language), what happens if someone other than the intended recipient answers the phone, how many times they call attempts will be made, etc.

if eligibility information will be obtained, the following is required in addition to the above:

- A statement that these question will help determine basic eligibility (complete eligibility may be determined in the future)
- What sensitive information will be collected
- What will happen to that screening information
  - How long data will be kept, who will have access, how information will be kept confidential, what happens with data if the subject chooses not to enroll
- A statement that the individual can stop answering questions at any time, and that their refusal to answer or participate will not affect their care at that institution/with their provider

Referrals from Colleagues (Referral Letters)

Description: Sending letters detailing the study to the investigator's colleagues, including contact information if patients are interested in participating or have questions. (IRB-approved fliers or brochures may be sent along with this letter for the colleague to give to potential subjects).

IRB Review: Must be mentioned specifically in recruitment section of study protocol. Letter template may not require IRB approval (check with local IRB). Fliers, brochures, etc. to be given to potential subjects do require IRB review. Remember to send to your IRB in a format that can be edited (e.g. Word, not PDF) in case edits need to be made.

Contents: Should include:

Name of PI

How the patient's information was obtained

Description of study, procedures, and time commitments (how many visits, how long each visit is, etc.)

Contact information for questions/participation

Notice that participation is voluntary

Departmental letterhead

Signature of someone involved in patient's care

Template:

a) in study protocol:

"The PI may also send letters to colleagues that detail the study and ask for their referral of potentially eligible subjects. In this event, letters will be submitted for IRB approval before use. Any other recruitment material to be included with that letter, such as a flier, will also be submitted for IRB approval."

b) letter template:

Date

Colleague's Name

Address

Re: (Condition) Research Study

Dear Dr. _____,

Dr. _____ at (name of institution) is currently studying (condition, "a new medication" for condition, "a new treatment" for condition, etc.) We are writing to inform you of the study so that you can share study details with any potentially interested patients. The study involves being randomly assigned to one of two treatments, one of which is experimental while the other is placebo/current medication/coming to (institution) once a week for blood draws/etc. Study participation will involve at least X number of visits over X time (days/weeks/months).

Subjects recruited from your practice will be returned to you for ongoing care. Please share the included recruitment materials with any potential, interested patients.

If you or any of your patients have any questions regarding the study, I/the study team can be reached at (contact information).

Thank you so much for your help.

Sincerely,

(name and signature of colleague)

Fliers

Description: Small posters detailing basic study information that include contact information for potentially interested subjects. Usually contain tear-off slips with contact information. These may require local permission for posting (e.g. ask a restaurant, office, or school first before posting the flyer).

IRB Review: Must be mentioned specifically in recruitment section of study protocol, including where the fliers will be posted.. Fliers must also be reviewed by the IRB. Remember to send to your IRB in a format that can be edited (e.g. Word, not PDF) in case edits need to be made. Upon approval, the IRB may return the flier in PDF format with the institution's IRB approval stamp. Only fliers with this stamp can be used, unless otherwise indicated by your IRB.

Contents: Should include:

- Names of institution, department, sponsor, PI, contact person
- Purpose of research (cannot use "new treatment" or "new medication;" must include word "research;" must indicate that drug/procedure is investigational and for research purposes)
- May briefly describe study/eligibility in the form of a question ("Do you suffer from dry eyes?")
- Cannot be coercive (e.g. should not emphasize compensation or efficacy of drug)

May state that subjects will be compensated, but cannot indicate a number

- Format and color should be appealing, text should be minimal and brief
- Contact information for questions or interest
- Funding information (if required by grant or sponsor)
- Protocol identification number assigned by IRB
- Tear-away slips at bottom (PowerPoint is recommended to make fliers; make the tabs/slips by inserting a textbox and rotating 90 degrees)

- Suggested locations: hospital cafeterias, departmental bulletin boards, waiting rooms, near elevators, restaurants, universities, etc. (please ask permission!)

Template:

a) in study protocol:

"The PI may also send letters to colleagues that detail the study and ask for their referral of potentially eligible subjects. In this event, letters will be submitted for IRB approval before use. Any other recruitment material to be included with that letter, such as a flier, will also be submitted for IRB approval."

b) flier template:

INSTITUTION
LOGO

Study Protocol
Identification
Number

Experiencing (CONDITION) Symptoms?

Participate in a research study for (condition)!

PURPOSE: To test Y as a potential treatment for X

(Insert image of something related to study- e.g. picture of related symptoms or someone of study-specific age, etc.)

Funding Source: (include NIH/grant funding if required)

Interested? Contact (NAME OF PERSON)

PHONE NUMBER • EMAIL

X Study
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Media Advertisements

Description: An ad placed (usually paid) to inform potential subjects about a research study, complete with contact information. May be visual (internet ad, newspaper, billboard, subway, bus, etc.), audio (radio), or video (television). Online ad services, such as by Google or Facebook, are useful in that they can be targeted to potentially relevant individuals (i.e. ads will appear to those searching for relevant terms).

IRB Review: Must be mentioned specifically in recruitment section of study protocol. The advertisement must be reviewed and approved specifically by the IRB. If the ad is visual, you may submit an image. If the ad is for radio, you may submit the planned script. Remember to submit to your IRB in a format that can be edited (e.g. Word, not PDF) in case edits need to be made. The IRB will also review the final taped/recorded ad.

Contents: Should include:

- Name of research facility and contact information
- Purpose of research (including condition/disease being studied)
- Basic eligibility criteria (i.e. age, gender, condition, etc.)
- Time required of subjects
- An indication that this is research (not treatment)
- Potential benefits (brief mention)
- May state that subjects will be compensated, but cannot indicate a number

Research Databases

Description: Study teams may keep a database of patients who have

previously indicated that they are interested in being contacted about clinical trials. These databases must be previously IRB approved, and individual authorization/consent is required from patients wishing to be included. Studies, under their own IRB approval, may refer to these previously (and separately) IRB-approved databases to contact potential subjects. The security of the database is the responsibility of the PI.

IRB Review: Must be mentioned specifically in recruitment section of study protocol. The database's protocol identification number should be referenced.

Template: "Potential subjects who previously indicated that they would like to be contacted about opportunities to participate in clinical research under (insert database's protocol identification number) will be contacted by the study by (mail, phone, etc.)"[6]

References

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Section 3

OBTAINING AND DOCUMENTING INFORMED CONSENT

Overview

The informed consent process ensures the protection of research subjects and enables clinical research to be performed ethically. It is the process by which a member of the research team presents a clinical trial to a potential subject, explains its purpose and design, illustrates known and predicted benefits and risks, and allows time for questions. Under the ethical principle of "Respect for Persons," the autonomy of patients and research subjects must be respected. CITATION: HALL Therefore, it must be the potential subject's will to participate in a trial and this must be documented. In order for them to properly consent, they must be fully informed of the trial and the requirements of participation. **Please ensure that the individual obtaining consent from the potential subject is allowed to do so per the IRB and the study's delegation log.**[1]

Supplies

For the consent process, you will need:

2+ copies of the consent. **The consent must be valid, i.e. bearing a stamp from the IRB and being the most recent, approved version of the consent.**

- 1 for the subject to read and sign a
- At least 1 extra for you to reference or as a duplicate

in case there is an error in the signing process

1 pen

1 clipboard or other writing surface

1 quiet, private room for a discussion with the potential subject

1 clock, watch, phone, or other method for keeping time

Setting

The consent process should occur in a private location, as sensitive health information may be reviewed (a patient's diagnosis or condition may be what makes them eligible for a trial). Though the more legal aspect of the consent process is the signing of the consent form, the form should serve as a reference in a discussion about the trial. Therefore, be sure to speak to the patient about the trial in a private setting, such as in the exam room after their visit. The potential subject may also want family or friends to be present for the discussion, so that they can also ask questions and understand the trial. After verbally reviewing the consent, the subject may want additional time to consider all of their options in addition to participating. You may want to leave them alone with the consent and with company to discuss and consider participation, or you may want to send them home with the consent to think over.

Describing the Trial

You must explain in full every aspect of the trial in the name of transparency and so that the potential subject can be as informed as possible before making a decision. Remember: they are likely not a clinician and have not been working on this project. Do not assume what the patient may or may not know, even about common medical terms and practices. The IRB requires that the written consent be written in plain, simple English that the average individual can understand; your verbal explanations for the trial should follow these guidelines as well. Remember to cover:

- The name of the trial

- What the project is investigating (a drug, a disease, etc.)
- How many study visits are required, how long they will be, and what procedures are involved
- The known and anticipated risks and benefits associated with participating
- Alternatives to participation
- Provisions and compensation for subjects
- Allow time for questions

In addition to allowing the *potential subject* to ask questions, the *member of the research team* should ask the *potential subject* questions to ensure their comprehension. The University of California, Irvine's Office of Research has developed suggested questions and tips for the consent process, which can be found at: https://www.research.uci.edu/compliance/human-research-protections/researchers/how-to-consent.html

Obtaining Signatures

Should the potential subject wish to participate in the study, the consent process is completed with a series of signatures on the informed consent form. **The order in which this is done is important and must be reflected in the time and dates recorded at the time of signature.** Though all parties should sign at the same time, it is rarely physically possible for several individuals to sign the same form at the same time.

- The subject signs, dates, and times at the allocated location(s) on the informed consent form.
- The member of the research team who is consenting the subject then signs, dates, and times at the allocated location(s) on the informed consent form. **The investigator's date and time cannot be before the subject's!**

- Depending on the study and the IRB, a third-party witness may be required to also sign, date, and time the form. This is especially true in instances where a non-English consent and translator are utilized.

Note: The subject is not enrolled in the study until all required signatures are recorded.

Completing the Consent Process

The subject should be given a **copy** of the consent for their own reference. They can use this primarily as a record of their participation, but also to refer to for trial and emergency contact information.[1] The **original** consent must be stored with study files in a secure location, preferably in the subject's chart. Remember, the document now has an individual's name and signature on it, and thus constitutes sensitive, protected health information.

References

1. How To Consent. 2015. (Accessed November 25, 2017, at https://www.research.uci.edu/compliance/human-research-protections/researchers/how-to-consent.html.)

Section 4

RESEARCH COMPLIANCE AND AUDITING

Compliance with federal and institutional guidelines for human subjects research and adherence to the IRB-approved protocol is essential for both subject safety and sound science. All members of the research team are charged with conducting research activities ethically and in accordance with Good Clinical Practice (GCP) guidelines, with ultimate responsibility falling on the PI.[1] These obligations include accurately recording and reporting all findings and events as they transpire. A free copy of GCP guidelines can be found on the FDA's website: https://www.fda.gov/downloads/drugs/guidances/ucm073122.pdf

Correcting Errors in the Study Record

Mistakes are often made when filling out forms, completing CRFs, or recording dates. In order to maintain the validity of the study record, correcting these unintentional errors must done transparently. The erroneous entry should remain legible for any member of the study team or for anyone auditing study records. Strike a line through your error and record the date and your initials. This way, anyone viewing the record will know who made the correction. Then, write the correct entry next to the original.

Notes to File

As noted in "**The Regulatory Binder and Essential Documents"** section, notes to file (NTFs) may be used to document protocol deviations and missing/incorrect documentation. They are often used to document such events as they happen and are included as a part of the study file so any member of the study team member or auditor has access to account of the event. NTFs can also be used

to record decision-making processes and communication with regulatory bodies (IRB, FDA, sponsors, etc.). NTFs are much more reliable than word-of-mouth recollection.[2]

Auditing

There are two kinds of audits in clinical research: those that are routine and those that are "for cause".

1. Routine: These may be performed at random by the IRB or the FDA (if a clinical trial under the FDA's jurisdiction) to ensure compliance with the study protocol, or may occur regularly as "monitoring visits" under the study sponsor and monitor (if there is a third-party sponsor for the study or if it is a multicenter clinical trial).

2. For Cause: Audits that are "for cause" are triggered in response to a precipitating event, such as an inordinate amount of protocol deviations or SAEs. This is done to ensure that the study team is following the approved protocol (and is therefore not exposing subjects to increased/undue risk). If a site has a particular high number of reported serious adverse events, they may be audited to determine whether or not the SAE may relate to the study intervention.[3]

Preparing for Audits: While standard monitoring visits for multicenter RCTs are typically scheduled in advanced, most IRB and FDA audits are usually announced 3-10 days in advance. Ensure that all study team members, especially the PI, are available to answer any questions and to provide access to study facilities and documentation. Make sure all study records are in order and are organized. Ensure that all forms have been completed, that all interactions with regulatory bodies are documented, and that all occurrences not otherwise captured in the study records have corresponding NTFs. You may need to reserve a private workspace for the monitor or auditor to review study files as study data is confidential and will include the private medical records of all study subjects (subjects waive HIPAA for research purposes and such situations when consenting for the study).

During Audits: While all study records are fair game for monitors and auditors, they tend to look at sensitive and essential documentation, including:

- Signed informed consent documents
- Records of study drug handling (receipt, storage, disposal, destruction, etc.)
- Documentation of all IRB/FDA submissions, approvals, and communications
- FDA 1572 Form (if a multicenter RCT under FDA guidance)
- Adverse event logs
- Subject medical records (to ensure study eligibility and complete documentation of medications, medical conditions, and adverse events)
- Study delegation log (to know who performs each study-related task)

While reviewing study files, auditors and monitors may find errors in the study files that need addressing or discrepancies between study documentation. Members of the study team must be available throughout the visit to respond and address any issues. At the end of the visit, the auditor or monitor will meet with the PI to review their findings. After the visit, the study team will receive a letter summarizing any findings and necessary corrective actions. This letter must be stored in the study file to document the auditing/monitoring visit.

After Audits: Items identified in the auditing/monitoring visit summary letter must be addressed in a timely manner. All items should be completed and accounted for within 2 weeks of receiving the letter. Per Dr. Judy Stone, the most frequent issues identified in FDA audits include:

- Lack of study team supervision by PI

- Failure to report and follow-up on AEs
- Failure to obtain IRB approval before modifying the study protocol and activities
- Failure to account for all study drug and subject doses

If there are serious concerns regarding compliance or good clinical practice, there may be repercussions for the study team: a follow-up visit may be scheduled, enrollment may be halted, or, in serious circumstances, all study activities will cease. Study activities may also be halted if a high frequency of a specific SAE is found to be related to the study intervention for the protection of subjects.[4]

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Chapter 7

PUBLISHING AND SHARING RESEARCH

Sharing the results of your research is arguably the most important step in the discovery process. It allows you to make your efforts known so that other clinicians (and their patients) can benefit from your work. Clinicians read publications and attend conferences to inform their clinical decision-making and practice. Contributing your work to these bodies helps to influence the field and allows for your own professional development. The era of evidence-based medicine relies heavily on peer-review. Proposed changes to healthcare and its delivery must have their worth proven and documented in the form of clinical research, and this research must also be vetted by the medical community. Peer-review ensures that the work is scientifically sound and has been performed ethically. Though the publication process may seem daunting, participating in academic medicine it is not only exhilarating and gratifying, but is also an ethical obligation for clinicians.

Recall that the ethical conduct of human subjects research requires that the benefit:risk ratio be maximized and that participants be respected. Modern research ethics require publication for both of these reasons and to benefit the field itself. When consenting to undertake the risks associated with a clinical trial, subjects enroll with the understanding that their efforts will be recognized both individually (through compensation) and across the discipline with the dissemination of results (publication). Many consent to research with the understanding that their sacrifices are for the greater good. The sharing of this newly found knowledge is also one of the anticipated benefits of a research project. Publication also inherently shows respect for persons by acknowledging those that volunteered to help obtain these results. Publishing in medical journals and

presenting at conferences will thus maximize your audience, allowing your project to be generalized.

Many are hesitant to publish their work. This may be because it is their first foray into research and they fear that their hard work will not be rejected by their colleagues in peer-review. This hesitance is more often born out of data analysis that reveals negative or inconclusive results, relating to the currently perceived "publication bias" which looks more favorably on papers with positive results.[1] Regardless of the results, whether positive or negative, disseminating your work at least saves colleagues from unnecessary redundancy; it updates the field as to what has been attempted and found. It should convince the community that such work need not repeating, thus conserving research-related resources.

Publishing also allows new clinicians the opportunity to be recognized by their peers and by their field. Promotions in academic medicine are often based on CVs and participation in academic activities, such as teaching, publishing, and speaking at conferences. While it may seem trivial to reduce a multi-year, grueling research project into one publication, citations are how academia measures productivity. Choosing the proper venue to share your research, whether by paper, poster, or conference, is thus the crucial last step in the research pipeline. This decision should be based on not only the perceived impact of your work, but also on its intended audience. Who do you want to know about your work? Is it relevant to a specific sub-discipline? Identifying the proper journal for your work may also spare you from several tiring rounds of rejection and revision, making the road to publication as smooth as possible. There are other decisions to be made in the publication process as well, such as authorship and selection of figures.

Assigning Authorship

Regardless which format you select for publication, authorship will need to be assigned. Several bodies, including the International Committee of Medical Journal Editors (ICMJE), have proposed guidelines for assigning authorship. Usually, the first author contributed the most to the project. There are some exceptions, however. In certain circumstances, especially when working in the lab

of a more senior PI, the last author is assigned the most credit. In this situation, the understanding is that the first author worked under the last author, and that the last author provided both funding for the project and the original idea.[2]

It is difficult to assign authorship when a large group works on a project. It is usually easiest to decide authorship order at the outset of a study.[3]

The ICMJE has proposed the following criteria for defining an author and their responsibilities:

1. Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data.

2. Drafting the article or revising it critically for important intellectual content.

Final approval of the version to be published.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.[4]

Care should be taken to ensure that all listed authors genuinely contributed to an article. The practice of "guest authorship," in which an individual who did not at all contribute to a project is given an author role as a favor, is heavily looked down upon by the scientific and medical community.[5]

If a unique order is chosen for authorship, or if you would like to thank individuals who are not authors for their work, this can be indicated in an "Acknowledgments" section.

Abstracts

Abstracts are used summarize an entire project, from background to discussion, in a simple block of text. They are also used to "sell" your project to the reader and encourage them to read about your work further. As Pearce and Ferguson note, "an abstract is

typically required when submitting a manuscript for publication, and is the format required to be considered for a conference presentation (poster, podium, or symposium) or for a grant application." The study's title and abstract are also used to identify and introduce papers in electronic databases (such as PubMed) and presentations at conferences. Abstracts are therefore ubiquitous in the world of academic medicine. They are can be difficult to write because they often require that complex study designs and medical terminology be distilled into 800 words or fewer.

An abstract should cover the background, significance, methods, and results. It should also strive to highlight the importance of the work, especially when being used to evaluate a potential manuscript for publication or a grant application. Pay special attention to your specific venue's requirements; these may vary in terms of word count and format. Some abstract formats are "unstructured," meaning individual sections (such as background, significance, etc.) do not have headers. It is therefore completely up to the author to fill the space (though there may be requirements). "Structured" abstracts will have section headers and will be less of a paragraph. Pearce and Ferguson have written an excellent paper on how to approach abstracts (it is available at https://www.ncbi.nlm.nih.gov/pubmed/28660736)

Abstracts can be written for projects that have either been completed or are still underway. In the former case, as will be used when submitting a manuscript for publication, the abstract should be written in the past tense. If the abstract is describing a project that is not yet completed, such as when you are applying for a poster presentation, items that have been completed should be addressed in the past tense and those that remain should be spoken of in the future tense. These are best written in an "iterative" process, meaning that the abstract is tweaked and tuned over a period of time and through a range of writing sessions. You should have friends and colleagues read the abstract, both people who are and who are not familiar with your project, to assess content and flow.[6]

Manuscripts and Papers

The matter of publishing should be discussed with the study

team even before a project begins. Authorship should be discussed and potential journals should be surveyed. In selecting a journal, keep in mind what audience you would like your paper to have. It is a basic science topic, or will it be relevant to a specific medical subdiscipline? Especially now, the age of online journals and open access, there are publications for almost every topic in medicine imaginable. Where there was once the "Journal of the American Medical Association" (JAMA) and the "New England Journal of Medicine" (NEJM), there is now also "Lupus Science & Medicine" and the "Canadian Hearing Report." Additionally, medical specialities and their professional communities will have their own, specific journals which may be a better choice instead of a more general medical journal. Speak with your research mentor or colleagues as to which type of journal would be most appropriate for your work, and which caliber.

Once you have selected a target journal, write according to their own specifications. Ensure that all of your images are as high resolution as possible to ensure that they are legible when printed. Remember to use a citation manager such as EndNote to manage your references (see Chapter 5, Section 3). Authors tend to approach manuscripts by writing the methods and results first. These sections are the most objective and therefore easiest to write. Addressing these early will also help you shape the rest of the paper, serving as a basis for what you may want to include in the introduction and conclusion. Much like abstracts, have friends, colleagues, and mentors proofread your paper. It should be the best shape possible before submission to reviewers, and it may be easier to take criticism from acquaintances than from a complete stranger.

The review process may vary from journal to journal. To better streamline the publication process in the age of electronic journals, the International Society for Medical Publication Professionals published an "Authors' Submission Toolkit" in 2010. It can be found at http://www.ismpp.org/index.php?option=com_content&view=article&id=34:mpip-initiative&catid=20:site-content&Itemid=111. Some journals will have their editors review papers, while others will employ "peer review," meaning your colleagues will be in charge of reviewing your paper. A paper may be immediately accepted, require requested revisions, or be flat-out rejected. When revising a paper, be sure to

address each comment. As the authors of the Toolkit remind its readers, "these reviews are intended to improve the manuscript, and are not meant as criticism."[7]

Some reviewers' comments will have easier fixes than others. Flaws in study design cannot be addressed with a simple rewrite. Try to be critical of your own work and note potential issues in study design or conduct in your Discussion section.

Posters

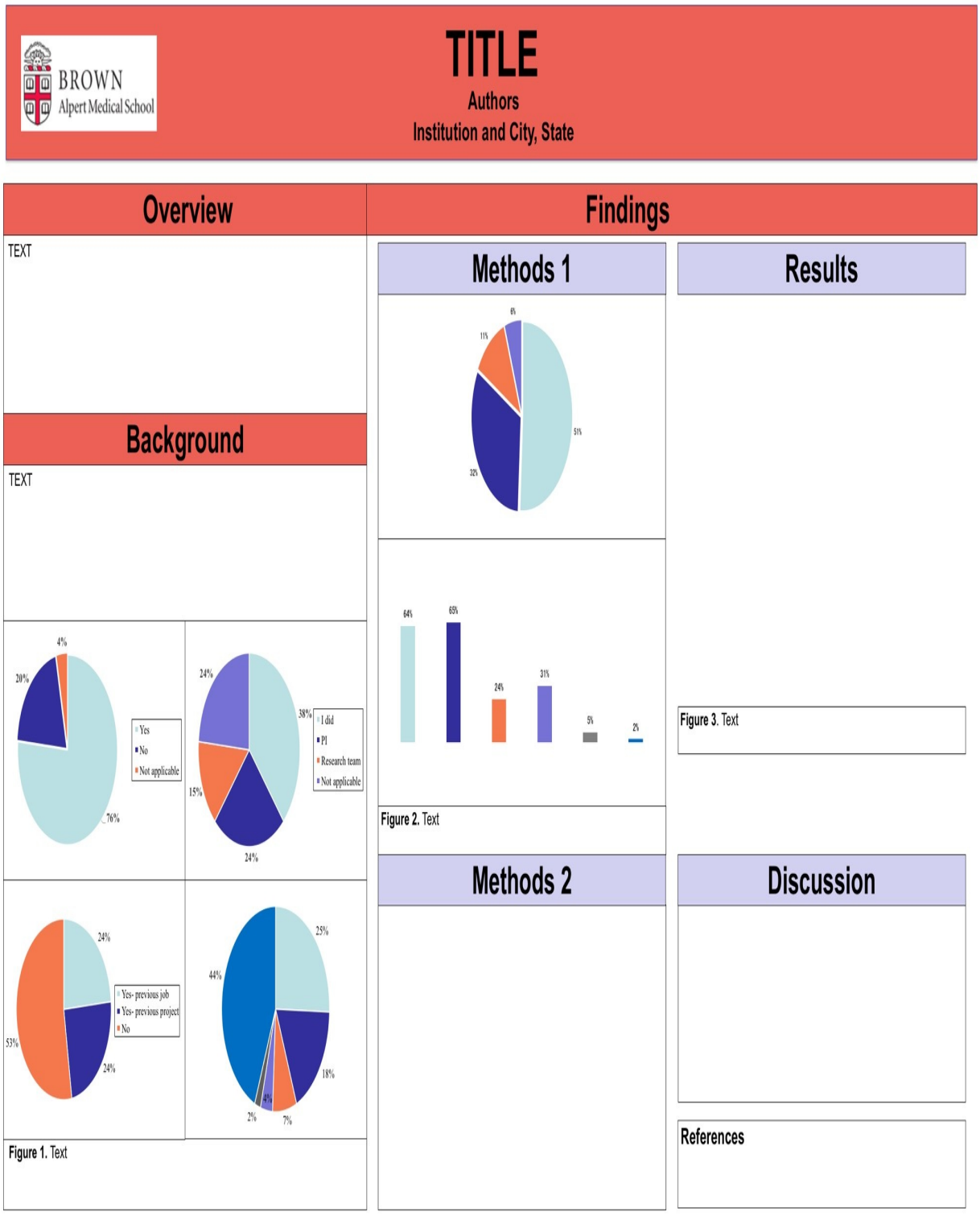
Posters are a unique publication medium in that they are a visual treatment. At conferences or conventions, they are much like abstracts in that they are designed to attract and invite interest in a specific topic. Posters are also usually used to share projects that are still underway, and will be a common publication methods for medical students and residents.

They should be visually appealing:

1. At a distance, to attract potential readers to come closer and learn more,

2. Up close, providing a satisfying visual display of your information information.

Because of their nature, posters rely more on figures than a written manuscript will. Images should be large and colorful with a high degree of resolution. Data may best be presented in tables, graphs, or charts, as the text should have much less of a presence than your figures. Posters can be drafted in PowerPoint as a slide with customized dimensions, depending on your conference or venue's requirements. Much like with abstracts, space and text are limited, but use as large a font as possible to ensure legibility both up close and from a distance at a conference. Logos for related institutions can be placed in corners to easily show who worked on the project and where it was done. A sample poster is included below.



Practice your elevator pitch for when standing by your poster and speaking with other conference attendees. Prepare responses to predictable questions- friends, colleagues, and mentors can help with

this. In 2011, Rowe and Ilic published an article identifying the pros and cons of poster presentations, as well as helpful tips and templates for the medium.[8] Their article can be found at https://www.ncbi.nlm.nih.gov/pubmed/21722851.

Presentations

Public speaking and being able to share research with large audiences are important skills in academic medicine. Actively participating in conferences and lecturing allow you to more widely disseminate your research, an ethical obligation in medical research, while also allowing the medical community to put a face to a name. Speaking publicly will also allow you to develop confidence as well as your professional image. You can also learn a lot from your audience, as members may ask questions that you have not considered or may present as potential collaborators for future research endeavors.

Much like posters, presentations are more visual. Slides should be made in PowerPoint and should not include any transitions. Figures and images should makeup the majority of your slide deck, as nobody likes a presenter who simply reads their slides. Be careful with color options for your text; black-on-white is best. You should only have as many slides as you can confidently get through in the allotted time. Like with poster presentations, practice your presentation and time it. The more familiar you are with your project and your slides, the more calm and confident you will be at the podium. You should be able to talk about your project as if the slides are not there, relying on them only for images but otherwise as little as possible.

Many presenters use similar slides at different conferences. In order to make a presentation as flexible as possible, suitable for a range of conferences and classrooms, many will keep a "master slide deck," which includes all slides related to a topic. You can then move the slides that you will use for that specific presentation to the front of the deck, and keep the extras at the end, separated from the "live" presentation slides by a few blank slides.

There are different strategies for outlining presentations. Some

presenters opt to present their project like a paper, beginning with the background and ending with future directions. Some present their work like a story, sharing their work chronologically. Though written for advanced practices nurses, an exceptional article on how to develop and deliver presentations was written by Kathleen M. Vollman in 2005.[9] It can be found at **https://www.ncbi.nlm.nih.gov/pubmed/15714019**.

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