3. Tips for an Institutional Review Board Application

An Institutional Review Board (IRB) is a group that has been formally designated to review and monitor biomedical research involving human subjects. The purpose of IRB approval is to protect the rights (including privacy and safety) and welfare of humans participating as subjects in research.[1] There is local variation in how individual IRBs manage applications. Investigators should contact their local IRB to determine the appropriate category for the application.

There are three different levels of IRB review for a research protocol, based on the type of research being performed: [2]

1) **Exempt:** Studies that have less than "minimal risk" to human subjects.
    - Example: Analysis of de-identified data.
2) **Expedited:** Studies that have no greater than "minimal risk" to human subjects.
    - Example: Analysis of existing records collected for non-research purposes in which subjects are identifiable.
3) **Full Board Review:** More than "minimal risk" to human subjects.
    - Example: Interventions involving physical or emotional discomfort or sensitive data.

Non-human subject research (e.g., a study utilizing archival deidentified data or a Program Evaluation) generally does not require oversight by an IRB, and this is often appropriate for economic analysis of telehealth interventions that have already been implemented to meet patient or health system needs. However, some IRBs expect that local investigators planning non-human subject research will apply for an "Exempt" determination rather than deciding on their own that the proposed study does not involve human subjects and may offer a simpler application process for this path. Many IRBs have office hours or an email address where investigators can ask for guidance before completing an application.

[1] Institutional Review Board Frequently Asked Questions. US Food and Drug Administration. Accessed 4/20/21. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/institutional-review-boards-frequently-asked-questions#:~:text=This%20group%20review%20serves%20an,as%20subjects%20in%20the%20research.

[2] Levels of IRB Review. Office for the Protection of Research Subjects, University of Southern California. Accessed 4/20/21. https://oprs.usc.edu/irb-review/types-of-irb-review/

IRB Applications

IRB applications can feel daunting but are manageable when approached in a stepwise fashion. Thinking through all aspects of a proposed study *before starting the application* is the key to a low-stress, efficient application process – this table provides an outline to guide investigators planning an economic evaluation of a telehealth intervention. (Although each IRB has a slightly different application format, the information that will be requested is generally the same as all IRBs are guided by the same federal principles.)

Topic	Overview	Example Language
Background	Provide a description of the problem or question that this study will address. Include a discussion of previous relevant research or data and any gaps in current knowledge to provide background and justification for the study. Explain the rationale/importance of this study and how it will contribute to existing knowledge. Include citations for references.	"Technology-dependent children have high resource use and do better in a home setting. Use of virtual care for this population is a promising modality based on prior studies showing XXX, but we to understand whether the intervention is economically beneficial from the patient, health system and/ or societal perspectives."
Research Question, Hypothesis, and Objective of Study	Explicitly identify the key question(s) or hypothesis being evaluated in this study. What is the objective(s) of the investigation? This section is best written with simple, goal-directed phrases. It should be a natural extension of the previous Background section. One primary outcome and 1-3 secondary outcomes are common, although the exact number will vary based on the study. All future sections in the application (i.e., the study methodology) should be designed to test the primary outcome. Economic evaluations should have an economic measure tied to the primary outcome. Secondary outcomes will usually, but not always, be tied to economic measures.	"The purpose of the study is to ____." **Primary Objective:** single, specific, addresses the main study question - Start with an action verb such as "to assess, determine, identify, evaluate, describe, compare, etc." **Secondary Objective(s):** specific study goals that will generate additional knowledge and are related to the primary outcome

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Study population	Detailed description of the population that is needed to test the primary and secondary outcomes, using inclusion and exclusion criteria. Larger, more diverse populations generally yield more broadly applicable results and may detect smaller, statistically significant differences. However, they also may include more confounders and will increase the effort (and cost) needed to collect and rigorously analyze the data. Consult a health care economist and/or biostatistician at this stage unless the research team is well-versed in economic evaluation study methodology. • Consider the likelihood and necessity of obtaining complete data sets for each individual in the study population. Consider studying a larger population if incomplete data sets may be used (i.e., approximately __ number of subject records will be reviewed in order to obtain ___number of evaluable subjects) • For multi-center studies: include the total number of subjects to be included across all sites and at each site. If site-specific subgroup analysis will be done to assess for geographic or local health care system/ market factors that may impact the results, it is essential to identify the minimum number of subjects required for each site to detect statistically significant differences.	**Eligibility Criteria:** *specific, tailor to primary/ secondary outcomes, define parameters, as applicable* **Targeted Study Population Size** (Total and Site-Specific if multi-center study) **Inclusion Criteria Examples:** • Gender(s) • Age Range • Diagnoses/ clinical conditions • Presence of specific lab or imaging findings • Received a specified telehealth intervention • Factors that affect telehealth usage such as access to broadband internet in the home or subject willingness to participate in virtual care (alternatively, these could be exclusion criteria if most subjects could reasonably be expected to meet a specific minimum requirements) **Exclusion Criteria Examples:** Diagnoses, conditions, physical examination, lab or imaging findings that are likely to confound the results or add study cost without commensurate benefit
Study location	Description of where the study will be performed, including all sites if a multi-center study. For telehealth, describe both the subject's location(s) and the clinician/ research team(s) locations if this is relevant to the study's design.	This study will be conducted at the following location(s): _____ If retrospective review, describe the subjects' location when data was collected.

Study design[3]	Briefly describe the study design and indicate how the study design will fulfill the objective of the study. Include designation of each of the following: • Descriptive (seek to describe) vs. analytical (seek to establish relationships) • Observational vs. experimental • Prospective vs. retrospective	**Example:** "This study is an observational, descriptive, retrospective chart review with paired payer claims database review."
Study methods	Describe (start to finish) how the interventions will occur (or has already occurred if a retrospective study) and how data will be collected. Include study period and data sources. **Date Range:** When choosing study period dates, consider if you want to include the ramp-up implementation periods that are common for novel telehealth interventions or if you only want to study an intervention in steady-state. It may be appropriate to evaluate the economic impact of a non-static telehealth intervention that is being iteratively improved via PDSA cycles if the implementation/ process details are unlikely to significantly impact the primary and secondary outcomes. Of note, there can be up to a 12-month lag between clinical care provision and finalization of payer claims. If payer claims data will be used, account for this lag when determining the Date Range for subject enrollment or retrospective Electronic Medical Record chart review. **Data Collection:** Describe any/all appropriate data collection method(s) for the study or describe the	**Example Language for Retrospective Studies:** "The study methods/procedures are limited to the review of existing medical records (or other data source)" **Data Sources** may include an Electronic Medical Record, departmental database, or publicly accessible database, among other options. **Date Range example:** "Data will be collected for subjects receiving XXX telehealth intervention between mm/dd/yyyy and mm/dd/yyyy" **Data Collection Examples:** 1. A list of potential subjects will be provided, and data will be manually extracted data from the electronic medical record. *Specify who will provide the report and how it will be provided* 2. A report from an existing database will be provided that will include all data required for this study. *Specify who will provide the report and how it will be provided* 3. Research personnel will personally run a report from an existing database or electronic medical record and manually extract data from the electronic medical record. 4. Research personnel will use data from a publicly available database

[3] Ranganathan P, Aggarwal R. Study designs: Part 1 - An overview and classification. *Perspect Clin Res*. 2018;9(4):184-186. doi:10.4103/picr.PICR_124_18

	methods including how the records to be reviewed will be identified and who will identify the charts to be reviewed. Describe any plans for entering data into any spreadsheets or computerized systems.	
Data Elements	Data elements to be collected should adequately describe the study population (e.g., demographics), including technology factors could vary among study participants (particularly if they are using their own technology/ devices), and measure the primary and secondary outcomes. If financial calculations will be performed during subsequent data analysis, determine what data elements are needed for the financial equations that will be used. Collect data in a format that will be easy to import into software capable of performing these calculations.	Create an example of the planned data collection spreadsheet or database and attach as an appendix. If there will be many variables, consider listing them or showing the data collection form/ tool in a separate, attached document.
Data Management	In this section, explain in detail how privacy and confidentiality will be ensured throughout the study. • If manually extracting data from Epic or a claims database based on a list of potential patients, describe where the patient list will be stored. • If using study identification numbers or codes, state that study subjects will be assigned a study identification number or code. • If you will be linking the study identification number or code to Protected Health Information in a master key or coded list, include which identifiers (Name, MRN, DOB, etc.) will be linked. Describe where the master key or coded list will be stored. Describe any plans for how and when the master key or coded list will be destroyed (i.e., after data analysis or study completed, shred box). • Describe how electronic data and/pr paper records will be stored. State whether they will be moved	**Data Storage Example:** "Data that includes personal health information (PHI) will be only accessible by study personnel, stored on a secure, password-protected server, and analyzed on a password-protected computer." **Data Sharing Example:** "A de-identified data set will be shared with a (institution name) biostatistician for the purpose of statistical analysis. The data will be shared via (state the method).State that study records and data will be retained per institutional research policies and procedures." **Privacy and Confidentiality Example:** "All study records and data will be kept private and confidential in accordance with Institutional policies and HIPAA. The investigators and other research personnel will not use study records and data for any purpose other than to conduct the study."

	from the primary/ patient study site listed at any time during the course of the study. • State which research personnel will have access to study records and data, and whether any data will be shared outside of your institution. If yes, state with whom and for what purpose. Include what data will be shared and how the data will be transmitted.	
Statistical Analysis	**Sample Size and Power:** • Indicate the sample size (number of records to be reviewed) • Provide rationale for sample size (i.e., sample size calculation or based on feasibility, comparable literature) **Statistical Methods:** • Include use of descriptive statistics or summaries and the statistical tests that will be used to evaluate study outcomes. • Describe procedures for accounting for missing data or outliers, as applicable. • Describe any procedures that will be utilized for quality control of collected data.	**Please refer to the separate economic framework toolkit document that was created for statistical analysis example language.**
Informed Consent/Assent and HIPAA Authorization	When Informed Consent (and assent for older children, if applicable) and HIPAA Authorization will be obtained, describe the procedures that will be used to obtain and document informed consent. NOTE: Remote/ virtual consent is increasingly used for telehealth studies, if allowed by the IRB. All of the following study conditions must be met to request a waiver of informed consent:	**Informed consent toolkits available from:** • https://irb.research.chop.edu/consent-templates • https://www.childrenshospital.org/research/irb/information-researchers/informed-consent

	• The research involves no more than minimal risk to the subjects • The waiver or alteration will not adversely affect the rights and welfare of the subjects • No sensitive information (drug use, history of sexually transmitted disease) will be collected. • The research could not practicably be carried out without the wavier or alteration • Whenever appropriate, the subjects will be provided with additional pertinent information after participation.	
Waiver of Informed Consent/Assent and HIPAA Authorization	**Waiver of Consent/Assent and HIPAA Authorization** In some cases, it is appropriate to request a waiver of informed consent. [4] In this section, describe how your study meets each of the regulatory requirements for waivers of consent/assent and HIPAA authorization. Some examples of practical and ethical reasons to justify a Waivers of Consent include: • The required study sample size is so large that including only those subjects/records/data for which informed consent can be obtained would impact the validity of the research or bias the study sample. • The subjects for whom records will need to be reviewed may be deceased, no longer patients or lost to follow-up and excluding these subjects due to inability to obtain consent may affect the validity of the research. • Disclosure of the study purpose in the consent process could potentially bias the research subjects and affect the research results.	**Example: Waiver of Consent:** "A Waiver of Consent/Assent and waiver of HIPAA Authorization are being requested for this study. The following provides justification for how the study meets criteria for Waiver of Consent and Authorization. This research study involves no more than minimal risk. The primary risk is breach of confidentiality. Safeguards will be taken to protect subject privacy and confidentiality as described in the Data Collection and Management Sections of the protocol. Protected health information will not be reused or disclosed by any other person or entity or for other research. No sensitive information (drug use, history of sexually transmitted disease, etc.) will be collected. Collection and use of protected health information will not impact the current care for patients whose data is used. Safeguards will be taken to protect subject privacy and confidentiality as described in the Data Collection and Management Sections of the protocol."

[4] 2018 Requirements (2018 Common Rule). Department of Health and Human Services. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html. Accessed 4/20/21

	• There is a risk to subject privacy and confidentiality by creating a link to otherwise de-identified data for the purpose of contacting individuals to obtain informed consent. (consent waiver only) • There is a potential risk that contacting individuals or families to obtain informed consent could cause emotional, psychological, social or other harm. • Data required to answer the research question is only contained in subjects' electronic medical records. It is not practical or feasible to obtain this information without accessing individual patient charts.	

Risks and Benefits to the human subjects	**Risks:** • All research studies have potential risks including physical, psychological, socioeconomic and legal risks. • Risks of a study may be categorized as not greater than minimal risk, minor increase above minimal risk or greater than minimal risk. ○ Minimal risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" • Describe any risks (i.e., breach of confidentiality) of the study. • Describe steps that will be taken to minimize risks (Example language: Safeguards to maintain subject privacy and confidentiality will be taken as described in the Data Collection and/or Management section(s) of the protocol). **Benefits:** Describe potential benefits of the study. In many cases, particularly in economic evaluation, there are no specific benefits to the study subjects, but there are societal benefits.	**Example of risks:** "Study activities represent no greater than minimal risk. The primary risk is breach of confidentiality. Safeguards will be taken to maintain privacy and confidentiality as described in the protocol." **Example of benefits**: "Since the study methods and procedures do not represent greater than minimal risk, unanticipated problems, including adverse events, are not expected. If any unanticipated problems related to the research involving risks to subjects or others occur, these will be reported to the IRB in accordance with Institutional and IRB policies." "The subjects whose charts are reviewed will not receive any direct benefit from the proposed research; however, there is potential benefit to society from the knowledge gained from this study, such as…"
Safety Management	Safety of human subjects must be addressed in IRB protocols, but economic evaluation studies represent minimal, if any, risk to the subjects. Language can be included to demonstrate to the IRB how you as the investigator will ensure that no safety risk arises.	**Example of minimal risk language:** "Since the study methods and procedures do not represent greater than minimal risk, unanticipated problems, including adverse events, are not expected. If any unanticipated problems related to the research involving risks to subjects or others occur, these will be reported to the IRB in accordance with Institutional and IRB policies."
Study Duration and Timeline	Describe the expected study duration and/or timeline for completion of the study. How long will this study take? Of note, this date range can be updated in the future with an amendment.	

References	List citations for all publications and presentations referenced in this protocol. In particular, include references to support the background and rationale.	
Appendices	This section may or may not be applicable, depending on the study. Some examples of appendices that you may want to include are listed.	• **Abbreviations and Definitions of Terms** • **Data Elements:** Include spreadsheet or data collection tool as a separate document. • **Coded Identifier List:** This is a list of unique subject codes and identifiers (name, medical record number, etc.) that will be used for the study.