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How to Conduct a Clinical Trial: Overview

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Abstract

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This chapter lays the groundwork for understanding the science of clinical trials. It is a primer on conceptualizing and operationalizing a clinical trial in dentistry. Subsequent chapters will address specific clinical areas and highlight methodological issues that are of particular importance to that discipline. In this chapter, we discuss critical initial steps in planning a clinical trial: developing a theoretical model of the problem, establishing specific objectives and hypotheses, articulating a theoretical model of the intervention, and establishing a scientific rationale for the study. After initial planning steps are achieved, there come the steps involved in protocolizing and financing the intervention: assembling an interdisciplinary team, establishing a study timeline, gathering an advisory group, choosing sites, budgeting and financing, obtaining study funding, obtaining clinical trial insurance, getting IRB (ethics) approval, addressing FDA and other regulatory issues, and registering the trial. Next comes preparatory work prior to the trial that involves staff training and certification including calibration and fidelity and establishing a study flow chart. The last steps are finalizing the trial design elements which include: allocation ratio, participant characteristics, recruitment protocols, intervention details, outcomes, advanced data collection considerations, sample size, randomization, blinding, statistical methods, data security, harms, limitations, generalizability, and publishing the protocol. Thinking about these steps far in advance will help you and your team iron out study details that are important in helping to answer your clinical questions and hopefully generate scientific evidence that can help to solve your clinical problem.

Keywords

Clinical trials
Efficacy trial
Effectiveness trial
Team science
Advisory group
Conflicts of interest
Clinical trial registration

2.1. Conception and Planning of a Clinical Trial

Theoretical model AQ1 of the problem

Specific objectives/hypotheses

Theoretical model of the intervention

Scientific rationale

Clinical AQ2 trials are conducted in order to answer specific questions about the efficacy, effectiveness, or safety of a clinical intervention. The intervention might be a new medical device, a drug, or a behavioral approach. Typically, trials are conducted in order to support or modify the standard of care. The results of randomized trials are considered the important level of evidence in developing practice guidelines and for the approval of medical devices and drugs. The levels of evidence and their importance are shown in Table 2.1. Efficacy questions address whether an intervention is able to produce the intended result. Often efficacy studies (often called phase 2 studies) are conducted in a single setting under the control of researchers and the participants are not fully representative of the intended population [1]. Effectiveness, on the other hand, in clinical trials parlance refers to whether an intervention is efficacious in the broad range of "real world" settings in which it is intended to be used and with a more representative group of participants. These are often called phase 3 studies or definitive trials. Normally, efficacy studies are conducted before a decision to carry out an effectiveness study. Nearly all clinical trials also address safety (sometimes called harms in the clinical trials literature) [2].

Table 2.1

Levels of evidence in descending order of strength by source of evidence[a]

Level	Source of evidence
1a	Systematic review of multiple high-quality randomized clinical trials
1b	Single high-quality randomized clinical trial
2a	Systematic review of multiple high-quality cohort studies
2b	Single cohort study; lower-quality randomized clinical trials
3a	Systematic review of high-quality case–control studies
3b	Single case–control study
4	Case series; poor quality cohort or case–control studies
5	Expert opinion

[a] http://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

Clinical trials are focused efforts and depend on the investigator having a clear model of the clinical problem being tackled. The need for an intervention should stem from a careful review of the literature regarding the disease, condition, or problem. Similarly, the choice of an intervention to trial should logically flow from the gaps or deficiencies in present interventions. Usually smaller scale formal studies (often called phase 1 studies or proof of principle studies) studies are carried out first to help clarify the need for and safety of a larger study [3]. Most importantly, the early studies allow for testing of procedures and measurement tools needed for a more advanced trial. They may also contribute to knowledge needed for defining a

hypothesized effect size, and for conducting a power analysis and determining sample size. Note, these studies cannot be ad hoc or poorly conceived or documented.

The key elements of any clinical trial protocol are the specific objective and hypotheses. These are stated a priori. An example from one of the author's work [4] is below:

Primary objective
• To determine if the test varnish containing fluoride and iodine is superior to a control varnish containing only fluoride in the prevention of new caries lesions.
Secondary objectives
• To establish that the response of child participants to the test varnish was not inferior to the control varnish.
• To document the safety of the varnish.

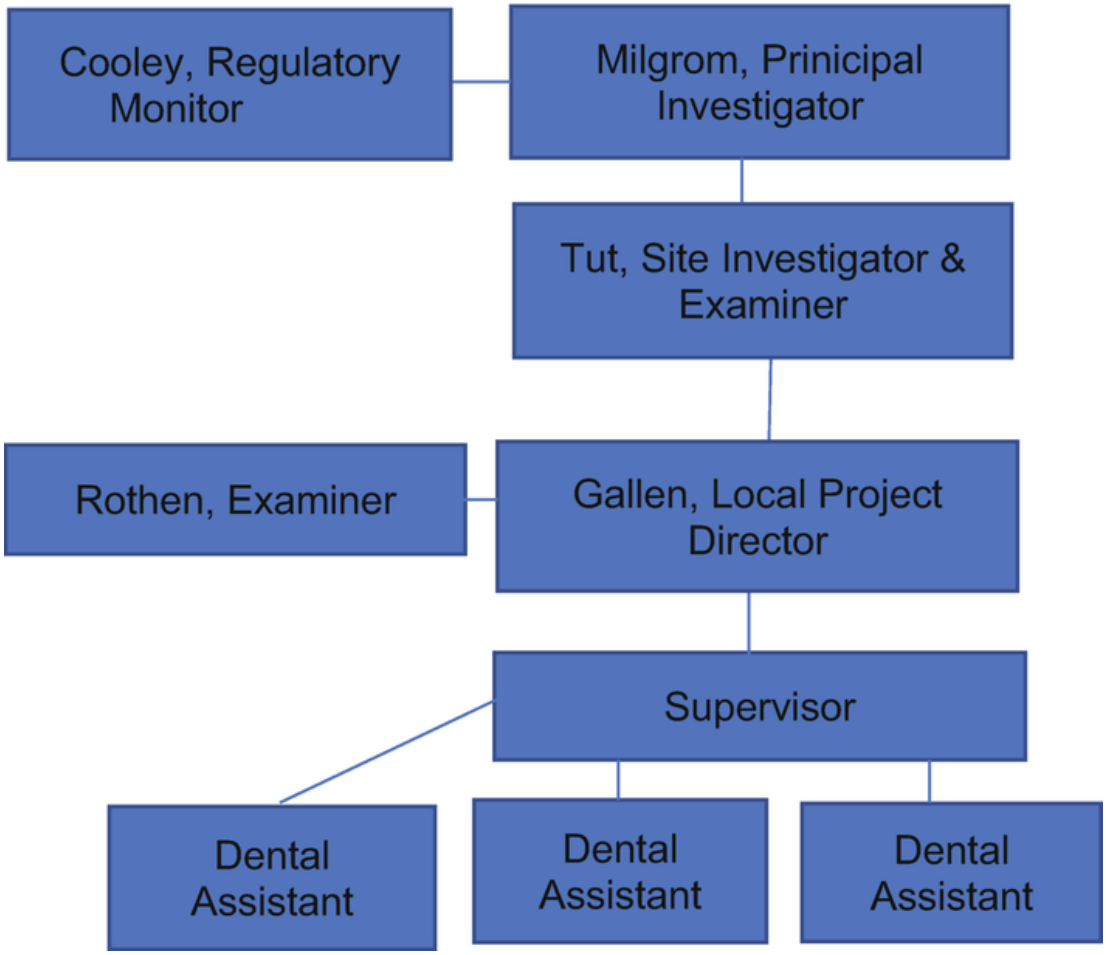
The hypotheses were that the test varnish is superior to an active control varnish containing only fluoride in the prevention of new caries lesions and that the child participants experienced no more anxiety during the application of the test varnish than when the control varnish is applied, and to document the safety of the varnish.

2.1.1. Assembling Interdisciplinary Teams

Conducting a clinical trial is not a solo effort but does require a leader, often called the principal investigator (PI). It is the job of the PI to lead the team and to coordinate and assemble the results of the efforts of the individual team members. PIs typically have final responsibility for all aspects of a clinical trial. A successful trial requires the collaboration of a team, with the duties and responsibilities of all members carefully delineated in the protocol and manual of operations. A clinical trial may require multiple sites to facilitate participant recruitment. A typical organization chart for a clinical trial is shown in Fig. 2.1. Many teams include expert clinicians, methodologists with expertise in measurement and instrument design, trainers, biostatisticians, data managers, and analysts. In situations where teams are incomplete, there are often gaps in the quality of the protocol or manual of operations, problems with measurement, or incomplete analyses. The process of team science is an emerging topic of scholarly interest [5, 6].

Fig. 2.1

Organization chart for a AQ3 recent clinical trial by one of the authors (PM)



2.1.2. Study Timeline

Clinical trials are lengthy. The study timeline includes (1) defining the objective and hypotheses; (2) gaining access to a study population and setting; (3) writing the protocol and manual of operations; (4) gaining ethical and regulatory approvals; (5) budgeting; (6) hiring and training staff; (7) accrual of the participant population; (8) carrying out the trial; (9) entering and checking trial data; (10) analysis; and (11) dissemination of the results.

An example of a trial timeline for a single site phase 2 trial one of us conducted of a new dental varnish is given in Fig. 2.2.

Fig. 2.2

Trial timeline for single site phase 2 study by one of the authors (PM)

Task	9/16	10/16	11/16	1/17	2/17	3/17	5/17	9/17	12/17	2/18	5/18	9/18	12/18	3/19	6/1/19	7/1/19	9/1/19
Government Site Approval Letter	X																
IRB approval		X															
Contracts			X														
Equipment ordered		X															
Equipment delivered				X													
Drugs ordered			X														
Drugs delivered				X													
Regulatory Site visits				X										X			
Staff hires & training				X	X	X											
Recruitment						X											
Exams						X				X				X			
Treatments							X	X	X	X	X	X	X	X			
Data Entry															X		
Analysis																X	
Reporting																	X

2.1.3. Advisory Groups

Historically, investigators used and abused the populations from which participants were drawn [7]. They are often described as "parachutists" who dropped in to conduct research and left without ever sharing the results of their work. This behavior engendered disbelief and anger and made carrying out clinical research in the same setting afterwards difficult. Today ethical researchers often have advisory groups drawn from the communities in which they are working, whether that be a clinic population or the population at large [8]. Indeed, some funders (e.g., the Patient-Centered Outcomes Research Institute in the United States) require formal community engagement plans and most granting agencies and foundations require dissemination plans (to be discussed later in this chapter). The individuals selected for advisory groups, who are typically paid for their time and service, can advise on the study from its conception through the actual interpretation and dissemination of the study results. Advisory groups need a structure and a formal job description. Members need leadership and need to know their obligations. The following is a typical charge to such an advisory group: providing community context on how the intervention might be perceived locally, identifying the most relevant outcomes that should be studied, helping to develop a participant recruitment strategy and problem solve during the trial, and playing a role in disseminating the research findings to local stakeholders.

2.1.4. Choosing Sites

Choosing a site or sites for a trial is one of the most important elements in planning. Successful clinical trialists have long-established bonds with the communities where they work. The communities are often underserved and have high rates of untreated dental diseases. We recommend to prospective researchers that they provide services in these communities for several years, to establish strong ties and friendships, prior to approaching community leaders or public health officials about conducting a trial in their community. Funders always request documentation of community acceptance prior to providing funding. Planning to gain community buy-in is always necessary.

There are many questions to ask oneself. Does the population have a high rate of the disease or condition I plan to study? Both of us have worked extensively in Alaska and the US-affiliated states in Micronesia [9,10]. Tooth decay rates in these communities are high. Is the population accessible—how difficult and time consuming will be it to recruit the study participants? One of us previously planned a study on the Navajo Reservation in New Mexico. The study center was to be in Gallup (a small city) but the population was spread over a 60 mile radius and included many tiny rural communities. This made planning difficult. Is the population large enough? Many of Alaska Native communities have populations of less than 1000. This makes the prospect of recruiting a sample very tough. Is the potential participant population typical of those who have the disease generally? We will discuss the importance of this element further later in this chapter. How transitory is the population—do they move a lot? How difficult will it be to find the participants when it is time to do follow-up exams or interviews, for example? How much loss to follow-up can be expected? A review of trials in major journals showed that 21% failed to achieve adequate numbers at randomization and 48% failed to achieve adequate numbers at outcome assessment [11]. Achieving the planned enrollment in a trial requires realistic planning, time and personnel, sufficient budget, and potential loss of participants requires inflating planned sample sizes. Failure to achieve planned sample sizes reduces statistical power to detect differences in study conditions and loss to follow-up diminishes the validity of the findings.

2.1.5. Budgeting and Funding

Budget periods for clinical trial research may include preliminary work and site preparation, the active research period, data entry and quality control, and dissemination. In our experience, most studies are under budgeted and the investigators run out of money at the dissemination stage. Also, complicated trials—especially those in the community—experience participant accrual rates below predictions—and often have to spend more time and money to successfully recruit the required population. Low accrual rates sink clinical trials, reducing their statistical power and excluding generalizability. Typical budget categories for clinical trials research include: personnel, consulting fees (including for advisory committees or a Data Safety and Monitoring Board [DSMB]), supplies and materials (including study drugs), incentives for participants, travel, and dissemination. Most institutions have formal written policies about how budgets are constructed and approved. Nevertheless, rarely has any functionary in the budget department ever directed a clinical trial so the accurate estimation of costs is the responsibility of the PI and the research team.

2.1.6. Funding

Clinical trials can be very expensive. Large multi-center trials in the United States or within the European Community can cost millions of dollars. Trials of dental caries preventive agents or treatments for periodontal diseases can last 3 or more years. Public funders might include states (e.g., in 2019 California allocated millions of dollars to public health work from the Tobacco Settlement program) or the national government. The National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, the Defense Advanced Research Projects Agency, the Health Services and Resources Administration, and other parts of the US government award grant funding for clinical research. A quasi-governmental agency, PCORI—the Patient Centered Outcomes Research Institute, gives funds for clinical trials. Parallel institutions exist in most countries, including the European Union and European countries, Japan, Hong Kong, Singapore, and the large states in Oceana, Australia, and New Zealand.

Private companies, particularly those that produce dental materials, and foundations also give grants to support research. Typically, however, the grants are small and support in vitro research. Very few pay the full cost of trials. Also, universities may place restrictions on commercial funding to assure the independence of the investigators and avoid actual or apparent conflicts of interest.

Reports of the outcomes of all clinical trials are required to include information on how the trial was financed and the role, if any, of the funders in the actual process of the research or interpretation of the findings. Historically, reporting of conflicts of interest in pharmacologic treatment trials was incomplete [12]. In academic institutions, investigators are required to file annual disclosures regarding potential conflicts of interest when trials are funded. The institutions may develop conflict management plans that specify what a conflicted investigator may or may not do within the research process.

2.1.7. Clinical Trial Insurance

Investigators working for large academic or public health institutions generally have insurance provided by their home

organization. It is important, however, for the prospective investigator to understand the nature and extent of the coverage and, under what circumstances, the investigator themselves might be responsible for unforeseen damages. The home institution may also self-insure. It may be useful to contact the risk management office or official within the institution. Information about liability insurance will certainly be required for constructing consent forms and gaining ethical approval. Funders, such as foundations or government agencies, may also require proof of insurance.

Trials sponsored by industry or otherwise privately funded may require commercial insurance for liability or errors and omissions. They typically cover claims related to participant injury, adverse effects, and errors by trial employees. Such insurance may also cover work-related injuries of employees. Working in remote areas, as we have, sponsors may require evacuation insurance to insure study employees can be transported should they have a serious accident on the job. Examples requiring evacuation might include a serious road accident on a remote island site in the Pacific or a snowmobile accident when a study employee was visiting a village site to see participants in rural Alaska in winter. This kind of insurance may be needed to supplement personal insurance that is provided as part of general employment contracts. In a tooth decay study, one of us completed in a rural area involving about 300 children over 2 years. The commercial insurance costs alone exceeded US $5000 (2019 dollars) per year.

2.1.8. IRB (Ethics) Approval

Worldwide there are ethical rules governing the involvement of human subjects in clinical research [13]. The principles are articulated in the World Medical Association Declaration of Helsinki in 1964 and augmented periodically until today. They build on the International Code of Medical Ethics. The principles make clear that "considerations related to the well-being of the human subject should take precedence over the interests of science and society." Moreover, in most countries, these principles are codified in laws and regulations regarding all aspects of clinical research. All reputable scientific journals require evidence that the protocols of published clinical trials adhered to the Helsinki Declaration principles and no trials can be published without such evidence.

In the United States, the policy for protection of human subjects is called the "Common Rule." It was first published in 1991 and is codified in section 45 CFR part 46 of the Code of Federal Regulations. The parts include rules for the protection of all subjects in research as well as special protections for pregnant women, human fetuses, and neonates, prisoners, and children. Universities in the United States are charged with assuring that academic scholars follow these regulations. They do this by mandating training for investigators and by hosting federally licensed Institutional Review Boards (IRB) that carefully scrutinize research protocols before approval and monitor on-going research to assure the protection and welfare of research participants.

Institutions can provide required human subjects protection training or they can provide access to subscription-based national training resources. The not-for-profit Collaborative Institutional Training Initiative (CITI Program, URL: citiprogram.org) provides comprehensive human subjects training and is widely used by the major US academic institutions as well as industry. Courses are largely on-line and cover both medical device, pharmaceutical, and behavioral research as well subjects such as biosafety and biosecurity, conflicts of interest, and Good Clinical Practice (GCP). CITI also offers frequent webinars on related topics. Training is generally required for any investigator or staff member who will have contact with human subjects or will be handling protected information.

Employees of academic and research institutions in the United States generally apply to their own institution's IRB for approval of research. Approval is not required at the stage where an individual is seeking funding but rather when funding is secured. Government agencies in the United States will not release funds for research without documentation of IRB approval. Very often the institutions provide training for investigators to aid them in completing the process. When more than one institution is involved in clinical trial research, such as in a multi-center trial, a single institution takes the lead in reviewing and supervising the trial. Institutions generally have agreements that govern the collaborations. Also, there are independent IRBs that focus strictly on industry-supported clinical trials. Investigators at academic institutions should consult with their own IRB as well as sponsors in determining the appropriate IRB of record.

Research conducted outside the United States is also subject to review. Principal investigators should plan far in advance to determine the nature of and comply with local review policies while also recognizing that their home institution generally must approve their work.

2.1.9. FDA or Other Regulatory Issues Including Trial Monitoring like DSMB or CRO

Phase 3 clinical trials have a DSMB [14]. Phase 1 or 2 studies may have a DSMB depending on the potential risks involved to participants. The DSMB consists of researchers, ethics experts, and statisticians outside of the study team and may be appointed by the investigator or the sponsor. In the case of studies sponsored by the National Institutes of Health, the DSMB is appointed by the PI with the concurrence of the program official. DSMBs are usually empaneled before the study commences and serve until the data are analyzed and reported. The DSMB receives annual reports on the progress of the study and has access to blinded reports on outcomes and adverse events. DSMBs will have a written charter specifying the duties of the members. The primary focus is participant safety. Recommendations are made to the Sponsor and Principal Investigator. A DSMB may recommend a study be halted prematurely. The DSMB is separate from the IRB, which maintains oversight.

In clinical trials under the purview of the FDA and similar governmental organizations throughout the world, the Sponsor will provide the agency with a copy of the DSMB charter.

Contract Research Organizations (CRO) are commercial companies that provide support to researchers and the industry on a contract basis. In the context of a clinical trial, the CRO may aid the investigator in organizing, managing and securing trial data, and in auditing the data quality. CROs typically make visits prior to study initiation, send staff to audit the completeness of records, and conduct monitoring visits. CROs issue formal reports that become part of the trial record. National Institutes of Health contracts with CRO organizations for this function. Similarly, a commercial sponsor may contract with a CRO to manage a trial but in this case, the CRO may also be advising on the overall management of a new drug or medical device application before the FDA or similar organizations in other countries. CROs vary considerably in size and scope of work.

DSMB members are typically compensated for their time and receive allowances for travel and other expenses in carrying out their duties. A PI must plan for the expenses of a DSMB within the study budget. In most cases, the Sponsor is responsible for the cost of using a CRO but how this is handled varies.

2.1.10. Registration of Trial

Virtually all scholarly journals today require that reports they publish represent clinical trials that were registered in advance of enrollment of participants. There are two key reasons. First, this protects against what is called publication bias. In this situation, authors—particularly those testing commercial products—only publish positive results and inflate the effectiveness of medical devices and drugs. Or, they may hide adverse effects. Without registration, the negative trials are in the shadows. Second, the registration of the study objectives, methods, and analysis plan establishes an a priori commitment to the outcome measure. Otherwise, there is a tendency of investigators to pick and choose among outcomes to report, after they have analyzed the data. Reporting quality continues to be low even after registration requirement policy implementation at journals [15].

Internationally AQ4, the World Health Organization International Clinical Trials Registry Platform (ICTRP) [16]. Trials registered at ICTRP receive a Universal Trial Number (UTN) which is then included in publications from the trial. Table 2.2 describes the 24 elements of the Trial Registration Data Set [17]. Some individual countries have registries that partner with the ICTRP.

Table 2.2

Elements of the World Health Organization Trial Registration Data Set[a]

1. Primary Registry and Trial Identifying Number
2. Date of Registration in Primary Registry
3. Secondary Identifying Numbers
4. Source(s) of Monetary or Material Support
5. Primary Sponsor
6. Secondary Sponsor(s)
7. Contact for Public Queries
8. Contact for Scientific Queries
9. Public Title
10. Scientific Title
11. Countries of Recruitment

12. Health Condition(s) or Problem(s) Studied 13. Intervention(s) 14. Key Inclusion and Exclusion Criteria 15. Study Type 16. Date of First Enrollment 17. Sample Size 18. Recruitment Status 19. Primary Outcome(s) 20. Key Secondary Outcomes 21. Ethics Review 22. Completion Date 23. Summary Results 24. Individual Clinical Trial Participant-Level Data Sharing Statement
[a] http://www.who.int/ictrp/network/trds/en/

In the United States, clinical trials are registered with ClinicalTrials.Gov [18] administered by the US National Library of Medicine, part of the National Institutes of Health. Section 801 of the Food and Drug Administration Amendments Act of 2007, known at FDAAA 801, requires registration of clinical trials and their results where the studies involve medical devices, drug, and biologics. Data element definitions, templates, and checklists are available on the clinicaltrials.gov website. The required data is similar to that of ICTRP.

Neither registry charges a fee. Both are searchable electronically.

2.1.11. Staff Training and Certification Including Calibration and Fidelity

A critical part of trial planning and execution is formal staff training [19]. This is true whether the objectives of a trial involve testing a medical device or drug or a behavioral intervention. The protocol will outline the training objectives and general approach to training. The Manual of Procedures will contain the specific instruction that is carried out. During the recruitment phase, research staff members may be screening participants and obtaining informed consent. Often investigators prepare scripts for staff members to learn and follow. These scripts become part of the official trial record. They are designed to be sure that informed consent procedures approved by the IRB are adhered to. This is particularly important in behavioral trials where staff members may influence the outcome of the trial by what they say.

In large or complex trials, the PI may ask staff members to complete an examination regarding study procedures including documentation and data entry requirements. Others, particularly in behavioral studies, will have staff members practice procedures under supervision and use checklists to evaluate and guide the correction of behaviors. These activities result in formal certification that the staff members are prepared to carry out the study, strictly following the protocol. Longer studies have periodic retraining.

In clinical trials where the outcome to be measured is a clinical oral health measure such as the Periodontal Index, the International Caries Detection and Assessment System (ICDAS) or reading the results of a dental radiograph, training, calibration and assessment of examiner agreement or reliability is required. The training usually includes required reading and memorization of codes, practice with a skilled examiner, and then a calibration exercise in which the results of examinations are compared with a gold standard examiner. The exercise needs to include sufficient numbers of participants that are typical of the population to be recruited. Ten to 20 participants are needed. In this exercise, both the trainee examiner and the gold standard examiner assess the same participants. The study biostatistician will then calculate measures of examiner agreement. This may be an Interclass Correlation Coefficient (ICC) when the measure is continuous or Cohen's or Fleiss' kappa when the measure is ordinal or nominal. The method chosen may also depend on the number of examiners. The large statistical packages used in science today include programs for assessing agreement. Most studies have initial training immediately before baseline data collection and then have refresher training and calibration before follow-up. Reports of clinical trials are required to include the results of the examiner agreement.

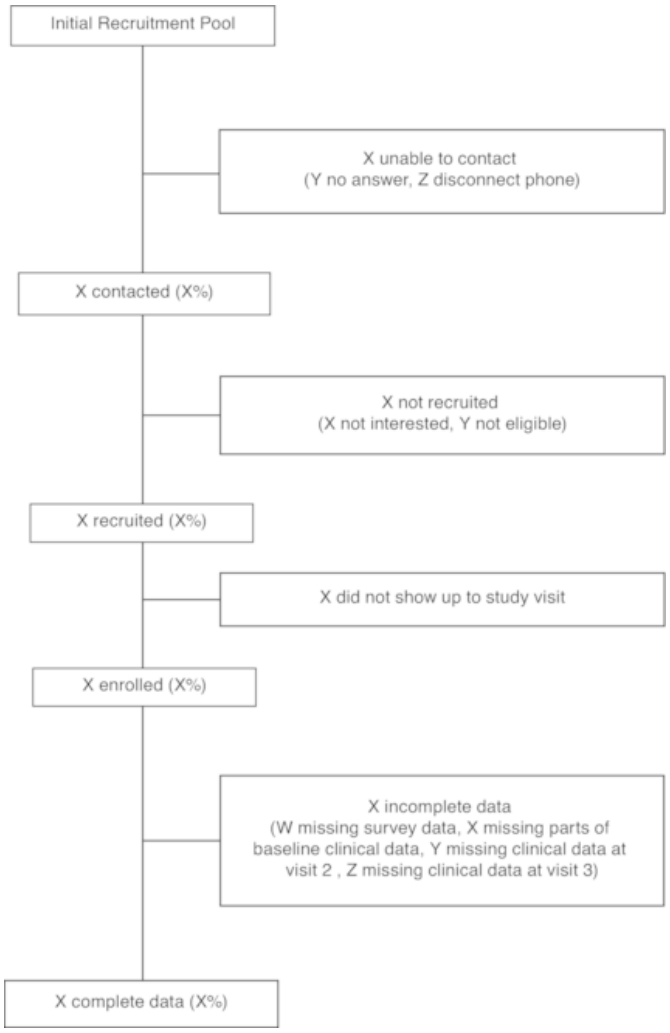
If recorders are to write down scores vocalized by examiners, the recorders should be trained and should be used in the calibration exercise as they would be used in the actual trial data collection. Examiners should review the written results to be sure the recorder is collecting the data accurately. Studies where data are entered onto a tablet computer or similar electronic device also require training and testing. These devices are often programmed so that out of range or inappropriate codes cannot be entered.

2.1.12. Flow Chart

It is helpful in planning a trial and conveying to potential funders or regulatory reviewers how the trial will be carried out to construct a flow chart. Figure 2.3 is an example of a participant flow chart. The flow chart schematically shows the visits a participant will make and the procedures, treatments, or assessments to be carried out. The IRB may use the information in the flow chart to assess participant burden and determine whether it is reasonable and justified. Similarly, the flow chart is helpful in assessing staffing needs and planning the budget. Flaws in a protocol can oftentimes be recognized after reviewing a flow chart. Templates for constructing flow charts are widely available.

Fig. 2.3

Sample AQ5 trial flow chart



2.2. Trial Design Including Allocation Ratio

Many trial designs are possible and the choice of a design depends on the study objective and hypothesis. A typical example of the statement of a design might be "This is a single center randomized, double-blind, placebo-controlled, parallel-group trial." A common element in studies of dental caries in children is a cluster-randomized design. In this case, children are clustered in schools and the schools become the unit of randomization. A design such as this might be chosen to avoid carry-over effects or because it is more efficient to do only one treatment at a given school. Cluster randomization may be less efficient than simple randomization because the analysis has to take into consideration within cluster correlation.

The statement of the design should also include the allocation ratio of participants between the active treatment and the placebo. Most often the allocation ratio is 1:1 because it is statistically most efficient. It requires the fewest participants to power the trial. Unequal allocation may be used in an initial safety evaluation of a drug or device to maximize knowledge gained about adverse effects. Investigators may choose unequal allocation because they perceive that more participants will join a trial if they have a good chance of getting the active treatment. There is little evidence that this helps recruitment and

can result in bias. If there is genuine uncertainty about what treatment is better, called equipoise, then there is no good scientific or ethical reason to have unequal allocation. To obtain the same power, a trial with unequal allocation requires 12% more participants if the ratio is 2:1 and 33% more participants if the ratio is 3:1. Reports of trials must include a statement of why unequal allocation was chosen. Regulators are likely to require justification for trials with unequal allocation ratios.

2.3. Participants

2.3.1. Eligibility

The protocol for any trial includes a formal statement of participant eligibility. This may include age, sex, language spoken or read, level of education, health status, dental condition, or other similar information. The protocol will specify exactly how each element is to be measured, how it is collected (for example, in person or over the phone), and who will collect it.

2.3.2. Exclusion Criteria

Similarly, the protocol will specify who and why a potential participant is to be excluded. This might be because someone is participating in another study currently, because they might move and be unavailable for follow-up, because they are allergic to a study medicine, or because they have a medical or dental condition that complicates their participation such as when individuals are receiving chronic antibiotic treatment that would complicate interpretation of effects from dental caries or periodontal disease treatments.

Effective trialists record the number of contacts with potential participants and the number and rate of inclusions and exclusions.

2.3.3. Settings and Locations Where Data Are to Be Collected

The trial protocol should specify the settings and locations where data are to be collected. When working with clinics, schools, or in other similar settings—particularly those away from the investigator's home institution, funders, and the IRB typically expect to see a formal letter indicating that those who control access to the site have reviewed the purposes of the study and have given permission for their site to be included. Potential investigators need to plan ahead of time for obtaining such letters as each individual site will have its own procedures for giving consent. In a clinic system, this might be reviewed and approved by a research committee. In a school system, teachers, principals, and the school's legal counsel might weigh in. In other settings, approval by a community advisory committee may be required.

2.4. Recruitment Including Dates

2.4.1. Planning for Accrual Problems

Inadequate and slow accrual or enrollment of participants is the primary reason that trials fail. Falling short may mean that a trial is underpowered. A DSMB or funder may halt a trial if accrual is inadequate. Planning for a trial often includes pilot work to provide evidence that the recruitment procedures and schedule are workable. For example, if a trial is to be carried out in a school and consent forms are sent home with the students, what rate of return of signed consent forms is anticipated? Will it be adequate? Is there a sufficient number of individuals that meet the recruitment inclusion criteria? Slow accrual is a budget buster. A back-up plan is always needed. Are there additional sites available? Will an advertising program help?

Trialists always record the beginning and end dates of recruitment. They often plot accrual rates and have regular meetings with research staff to review the progress of recruitment. If recruitment is problematic, they initiate backup plans before it is too late and they run out of funds, time, or review groups or the sponsor cancels the study.

2.5. Preventing Attrition, Documenting Attrition

Loss to follow-up, also called drop-out or attrition, is another leading cause of trial failure. Sample sizes are usually inflated to anticipate a certain rate of loss to follow-up. This may because, for example, older adults die before being able to complete a study or because children change schools and cannot be found. Annual rates of attrition in US studies can exceed 10% or 15%. See, for example, a Cochrane review of clinical studies comparing the effectiveness of Atraumatic

Restorative Treatment versus conventional restorative treatment where multiple studies found to have loss to follow-up of 20% or more [20]. Because studies are powered to detect a treatment effect, loss to follow-up can result in an underpowered study where it is not possible to reach definitive conclusions about the efficacy or effectiveness of the study drug, device, or intervention. Note, the standard for trial analysis is "intention to treat." This means that data for each subject enrolled are included in the analysis, even if the participant dropped out. It is generally not permissible to report out trials where only data on those who finished a trial are included in the analysis as this result will be biased.

In reporting a trial, researchers need to document drop-outs or lost participants including when and why attrition occurred. Flow chart templates are available as part of the CONSORT Statement [21]. Many scientific journals expect that such a flow chart is submitted as part of the report of a trial. Similarly, the IRB, DSMB, and regulators will want to see this documentation.

2.6. Interventions

How and when administered

Details that can be replicated

Trial protocols specify the detailed nature of the treatment arms, whether they are devices, drugs, behavioral interventions, or placebos. They are described in sufficient detail so that the treatment could be replicated. The protocol will specify how and when the treatments are to be administered and who will carry them out.

2.7. Outcomes

The trial outcomes are clearly specified a priori. That means the investigator has a hypothesis and that the study has been powered to detect the effect that this outcome represents. The time point at which the outcomes are measured is also specified a priori. This is especially important in blinded clinical trials because choosing the outcome after one sees the results can result in bias. Sometimes this is called the trial endpoint.

2.7.1. Primary

The primary outcome is collected to test the main hypothesis of the clinical trial. Examples of primary outcomes in caries studies might be the ICDAS category, the number of newly decayed teeth, or periodontal attachment or pocket depth. It also could be the presence or absence of an intraoral lesion or pain. It is possible to have more than one primary outcome but not a long list. Some studies have both a clinical outcome and a patient-centered or patient-reported outcome. Examples of patient-centered measures are pain reports, satisfaction, and quality of life.

2.7.2. Secondary

Studies sometimes have secondary measures. Often the study is not powered strongly to detect changes in the secondary measures but they be helpful in understanding the main trial outcome or may allow for exploratory hypothesis testing that will be followed up in future studies.

2.8. Advanced Data Collection

2.8.1. What Is Important to Collect and Why, Generalizability, and Mechanisms of Action

For trials designed to detect changes in disease prevalence or health behaviors, it makes sense to collect such data at baseline and again at the end of the intervention. This allows investigators to test the main research hypothesis—does the new medication prevent tooth decay or did the behavioral intervention help to improve the frequency of toothbrushing? However, there are opportunities to collect data at other time points to answer questions related to the main hypothesis. For instance, trials may require multiple years of participation and follow up, which could turn away some potential participants. In these instances, there is value in collecting pre-baseline data before a team recruits for the intervention (e.g., tooth decay). After recruitment is complete, having pre-baseline data would allow the team to assess the degree of selection bias,

interpret the main study findings, and determine generalizability.

Additional data can also be collected at other time points. If there is interest in identifying possible mechanisms driving an intervention, then interim data collection could be collected to measure these potential mechanisms (also called mediators) [22]. For instance, self-efficacy may be the hypothesized mechanism of a behavioral intervention [23]. Measuring self-efficacy at baseline and several time points during the intervention would result in longitudinal data to help test this mechanism hypothesis. When an intervention ends, there is the possibility of collecting data from participants to understand what went well and what parts of the intervention could be improved. Having these post-intervention data on hand could help the research team refine interventions for future testing.

Data collection plans require careful a priori attention to the conceptual model of the intervention as well as an understanding the effects of collecting additional data, like higher rates of participant dropout because of increased burden, extra staff time to collect the data, and costs of processing the data in the lab.

2.9. Sample Size

In planning a trial, investigators estimate the sample size needed to determine the difference between treatment arms. Trials may be superiority trials (e.g., the test drug is more effective than the comparison drug or a placebo) or equivalence trials (there is no difference between the arms). In superiority trials, the biostatistician uses pilot data or work from published studies to calculate the power, that is, the probability that a test of significance will pick detect a treatment effect that is present, that is, the probability of rejecting the null hypothesis. Power ranges from 0 to 1 and most clinical trials have sample sizes for testing the primary hypothesis with a power of at least 80%. Obviously, the better and more relevant the pilot data or data from other studies, the more likely the study will be large enough to find the treatment effect. Power calculations are specific to the type of analysis that is planned. Many studies are underpowered for assessing secondary outcomes. Power is reduced when there are interim analyses, such as when the primary outcome is at 2 years but the investigator also assesses the measure at 1 year.

Studies may have built-in stopping rules. Typically, this happens when the biostatistician finds that a treatment is particularly effective in an interim analysis and the DSMB finds that ethically the treatment should be available to all the participants. However, stopping a study early tends to over-estimate the effectiveness of the treatment being evaluated.

2.10. Randomization

2.10.1. Method

For most trials, simple randomization is sufficient. The study biostatistician can use any number of statistical programs to develop the randomization scheme. As discussed earlier in this chapter, the participant should have a known, usually equal, chance of being assigned to any of the treatment arms. Successful randomization requires that treatment assignments cannot be predicted in advance.

In practical terms, the biostatistician places the coded treatment choices in sequentially numbered closed envelopes, which are opened by the treating clinician only at the time of treatment. Or, in a study of school children, all of the children's ID numbers are assembled in a file and are assigned randomly to the treatment arm. Then, class lists are prepared with child's ID and treatment code. The children may be given color-coded cards or slips of paper that identify which treatment they are assigned to.

2.10.2. Type (e.g., Blocking, Stratification)

It is common that randomization is done in blocks. For example, a study conducted in schools may have assignments done separately for each school. The idea behind this is to make sure that bias is not inadvertently introduced into the study by having extremely unbalanced arms. Another example is where participants are first stratified by baseline dental caries score and then assigned to treatments within the strata.

2.10.3. Allocation Concealment (How Random Allocation Is Implemented)

In random assignment, allocation concealment prevents investigators from choosing treatment allocations for particular

participants. Imagine, for example, a clinical trial being conducted in doctor's offices. A participant who is enrolled in the trial may want to receive the new treatment. This kind of assignment would create bias and decrease the validity of the trial results and must be avoided. Allocation concealment involves not disclosing to participants and those involved in recruiting trial participants the allocation sequence before random allocation occurs.

2.10.4. Implementation (Who Will Generate the Random Allocation, Who Will Enroll, Who Will Assign Condition)

The trial protocol will specify exactly how the assignment of participants to conditions will be carried out. That includes, as we discussed earlier, the generation of random allocation, as well as who will enroll participants and who will actually implement the assignment.

2.11. Blinding

Blinding is the practice of not telling participants in a clinical trial whether they are receiving a placebo or comparison treatment. In an experiment, if the subjects in the control group know that they are receiving a placebo, the placebo effect will be reduced or eliminated and the placebo will not serve its intended purpose. Similarly, examiners and others working directly with participants or evaluating outcomes are kept blind. A double-blinded design means that neither the participant nor the investigative team are aware of whether the treatment received or being administered is the test device or agent or a placebo. In a pharmaceutical study with two treatment arms, the treatments might be labeled A and B. The definition of the codes is kept in a secure place by someone not involved in working with participants. Often the biostatistician is the keeper of the code. And, codes are typically not broken or treatments revealed until after the data are analyzed.

Behavioral studies may not allow blinding of participants or staff members administering the interventions. In this case, examiners are not informed of the assignments and collect outcome data in a blind fashion. As with drug or device studies, data may be analyzed before the codes are opened.

2.12. Statistical Methods

The biostatistician is a critical member of the investigative team. This individual participates in the design of the study and writing of the protocol as well as in the analyses of the data. Experienced investigators know that bringing in the statistician after a study is poorly designed is a big mistake. Generally, sponsors or funders expect that the team will include a biostatistician and country regulators, such as the FDA, are unlikely to accept studies done without such a person on the investigative team.

We advise new investigators to create mock data sets and attempt the planned analyses before any participant is enrolled or any data are collected. This allows the novice investigator to carefully assess whether the planned analysis approach will yield the intended test of the hypothesis.

2.12.1. Intention to Treat Versus Per Protocol

Primary tests of hypotheses in clinical trials follow the "intention to treat" principle. This means that every participant who is enrolled and for whom there are some data is included. Drop-outs and participants lost to follow-up are included. Reputable scientific journals will not publish the results of trials that do not follow this principle. In contrast, one can find many older studies—especially commercially sponsored studies—where the data were analyzed "per protocol." This means that only the data from subjects with complete records are included in the analysis of results. This biases upwardly the effects of the study agent. Sometimes, per protocol analyses are conducted secondarily to explore possible treatment effects when studies are underpowered.

It is beyond the scope of this chapter to address in detail the statistical approaches to analyzing clinical trial data. Nevertheless, clinical trials ask relatively straightforward questions and the first test of a hypothesis should be simple and unadjusted. The biostatistician will check the impact of randomization on the balance of the levels of moderators that might impact the strength of the effect of the treatment. Examples of moderators are age and sex. Within a caries study in children, for example, age may impact the number of teeth at risk or the length of time the teeth have been in the mouth and at risk. The randomization process aims to balance these factors within the groups. Randomization in caries studies is

often stratified by the number of carious lesions at baseline to avoid imbalance. Additional analyses may adjust for such factors. Also, regression models have been developed that account for the often skewed distribution of dental caries where many teeth or people have none or very low numbers of lesions. Models that include effect modifiers are useful secondary analyses to generate hypotheses for future research.

2.13. Data Security

It is the responsibility of the PI to maintain the security of clinical trial data. The security of personally identifiable data in the United States is governed by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). IRBs review plans for data security. Data forms and computer files contain identification numbers instead of participant names and the list of names and codes is stored separately. Paper forms are in locked cabinets and rooms accessible only to authorized investigators. Computer files are password protected. Studies regulated under the US FDA and many other government organizations must use data management systems. The standards are contained in Chapter 21 CFR Part 11 of the Code of Federal Regulations. FDA employs auditors who review the trial documentation to determine at the project level if a study is compliant. Data security and confidentiality are included in the training required of investigators and research staff members.

2.14. Harms

Study drugs or other interventions have the potential to cause harm. These unexpected outcomes are called Adverse Effects (AE) in formal parlance. AEs are different than known side effects. Table 2.3 describes the typical AEs that are collected in sophisticated clinical trials. Most AEs are unrelated to the study but are nonetheless captured in a consistent way. For submission of trials to country regulators such as the FDA, 24–48 h in-person post-treatment checks for all participants are desired. In other studies, participants may be sampled or follow-up may be done by telephone. Investigators are asked to assess the degree to which an AE is related to the study device or drug. Major trials have a medical monitor who reviews AE reports. The FDA and many other country regulators have strict requirements for reporting severe AEs in a timely way. Mild or moderate AEs are normally reported in annual reports to the regulator.

Table 2.3

Examples of adverse effects within clinical trials[a]

Adverse event	Mild	Moderate	Severe
Oral mucositis by exam (e.g., erythema, ulceration)	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake
Allergic reaction (e.g., difficulty swallowing or breathing, swelling around the lips or skin of the face, itchiness around the lips or skin of the face, hives, or rash)	Transient flushing or rash, drug fever <38 °C (<100.4 °F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 h	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Life-threatening consequences; urgent intervention indicated or death
Anaphylaxis	–	–	Symptomatic bronchospasm, with or without urticarial; parenteral intervention indicated; allergy-related edema/angioedema; hypotension Life-threatening consequences; urgent intervention indicated or death
Vomiting	1–2 episodes (separated by 5 min) in 24 h	3–5 episodes (separated by 5 min) in 24 h	≥6 episodes (separated by 5 min) in 24 h; hospitalization
Gastrointestinal pain (e.g., stomachache)	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL
Diarrhea	Increase of <4 stools per day over baseline	Increase of 4–6 stools per day over baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization

[a] Adapted from Advantage Protocol 2019-10-19 Phase 2 Efficacy & Safety Evaluation of Advantage Anti-Caries Varnish for Primary Prevention with permission. Sponsor Contact: Peter Milgrom, DDS

AEs are reported by organ systems and are internationally standardized. Coding is done by the investigator using the Medical Dictionary for Regulatory Activities (MedDRA) based on the AE reports after they have been reviewed by the study Medical Monitor [24]. Training is available on the MedDRA website and through courses and webinars offered to investigators and study staff. MedDRA are both downloadable and available online. MedDRA is under the direction of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). MedDRA is available upon subscription. The summary report of AEs should be included in the Harms section of published reports of all trials.

2.15. Limitations

As with the analysis, we often advise new investigators to write the limitations section of their report before the study is initiated. A study planner who is aware of the limitations of the approach chosen may elect to modify or enhance the design or at a minimum recognize what he or she will able to conclude from the study. The limitations include issues of reliability of measurement and limitations to internal or external validity.

2.16. Generalizability

2.16.1. External Validity and Applicability

External validity is the appropriateness of applying the conclusions of a clinical trial outside or beyond the context of that study. In other words, applicability is the extent to which the results of the study can be generalized to and across other situations, people, and times. A couple of simple examples of external validity issues may be illustrative. A big issue in drug research is the need to study treatments for children in children and not just adults. The FDA, for example, requires investigators to develop a Pediatric Study Plan providing assurance that children are included in the study population. A historical example is where gingivitis studies were conducted were conducted in male participants only, because investigators felt that effects of menstruation would interfere with the measurement of gingival inflammation. Results of studies not conducted on women may not be valid for women. These validity issues extend to race or to socioeconomic status as well.

2.17. Publishing the Protocol of a Trial

- Journal choices
- Peer review

Today many investigators publish the peer-reviewed protocols for trials. Journals have evolved that publish the protocols. Examples are Contemporary Clinical Trials, Trials, BMJ Open, and others. These papers go further than the relatively simple listings in the clinical trials registries. If the protocols have been formally peer reviewed, they often are not sent out for review again but instead published as written. This can provide a publication for younger investigators involved in trials who may have to wait several years before being able to have anything in the literature and whose advancement in academic settings might be impacted. Protocols that have not had formal peer review by a funder can still be published. In this case, the journals will follow their normal peer review process.

2.18. Publishing Results of a Trial

- CONSORT statement
- Journal choices
- Conflict of interest

The publication of clinical trials has largely been standardized internationally by the publication of the Consolidated Standards for Reporting Trials (CONSORT) [21]. The comprehensive CONSORT site provides guidance on the elements

required for a trial publication, extensions for different designs, and useful templates and checklists. The CONSORT Statement is endorsed by leading scholarly journals in dentistry and medicine. One should not submit a clinical trial report to a journal that does not endorse the CONSORT Statement.

A special concern in clinical trials of devices and drugs is conflict of interest. One has only to turn to the major newspapers to find reports of published research that may have been biased by investigators who have received, but not publicly acknowledged, payments or other rewards for their participation in research. Such investigators may hold patents or other valuable intellectual property. The peer review process is intended to secure the scientific integrity of the trial and report. Public disclosure of potential conflicts of interest are intended to clarify the role of conflicted individuals in the collection, analysis, or interpretation of trial findings. This does not bar individuals from participating in the publication of the research.

2.19. Case Scenario/Study Questions with Key

You are the Dental Director a large community health center that serves low-income populations. Over 90% of the adults in your clinic are enrolled in Medicaid. Most of these adults come in for regular check-ups every 6 months. However, many of the adults present with recurrent tooth decay at these check-ups. You and your staff have identified poor diet, particularly too much added sugar intake, as the source of the problem.

1. What are potential intervention strategies?
2. What is the importance of an advisory group? How would you assemble an advisory group?
3. What is your selected intervention and what is the main outcome?
4. How will you fund your intervention?
5. What are the steps involved in obtaining IRB approval for your intervention?
6. What type of special training will be needed for your study staff?
7. What are the inclusion and exclusion criteria for your intervention?
8. What is your participant recruitment plan?
9. How will you prevent attrition during your study?
10. What are potential harms of your intervention and how will you monitor for these during the intervention?
11. Complete the CONSORT Statement for your study.

2.19.1. Key

1. What are potential intervention strategies AQ6 ?
   - Chairside motivational interviewing intervention to improve diet
   - Home-based intervention to improve meal quality
   - App-based intervention to monitor and reduce added sugar intake
2. What is the importance of an advisory group? How would you assemble an advisory group?
   - See Sect. 2.1.3
3. What is your selected intervention and what is the main outcome?
   - Respond depends

4. How will you fund your intervention?
   - See Sect. 2.1.6

5. What are the steps involved in obtaining IRB approval for your intervention?
   - See Sect. 2.1.8

6. What type of training will be needed for your study staff?
   - See Sect. 2.1.11

7. What are the inclusion and exclusion criteria for your intervention?
   - See Sect. 2.3

8. What is your participant recruitment plan?
   - Chart review and direct contact
   - Fliers placed in waiting room
   - Recruitment in waiting room

9. How will you prevent attrition during your study?
   - Provide incentives for participation
   - Collect information on alternative ways to contact participant (e.g., phone, e-mail, text, contact for family member or friend)
   - Create social media page with study updates to keep participants engaged
   - Keep study obligations for participants simple

10. What are potential harms of your intervention and how will you monitor for these during the intervention?
    - See Sect. 2.14

11. Complete the CONSORT Statement for your study.
    - See Sect. 2.18

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