Chapter 4
Subject Selection

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General Concepts

Like the endpoints and the interventions in your trial, the subjects targeted for enrollment are initially proposed within your final primary research question. That's why it is critical to get the question right from the outset. Just a word regarding semantics of language. The terms "patient" and "subject" get used interchangeably when it comes to the individuals enrolled in clinical trials. Since we are generally proposing medical trials, all those enrolled will be patients of one sort or another, and it might be they are the very patients that generated the idea for the trial in the first place. However, the term "subject" is generally the preferred nomenclature for a patient who is enrolled into a clinical trial. It is an important distinction because the investigators are often not the medical caregivers for the subjects enrolled in the trial, and so separation is needed between the patient's general medical care and the reporting of a subject's participation in a clinical trial. I will use subject from here forward for consistency.

It is common for all of us to think that once we have a good research idea and have refined it into an actionable research question, finding subjects to enter into the trial will be easy. This can be an "eyes bigger than your stomach" phenomenon, and those more experienced have learned this perhaps the hard way. We all are guilty of thinking and even saying "we see 'a ton' of patients in clinic with disease X that would be amenable to intervention Y." This fuels an initial interest in developing the trial. However, a realistic, detailed appraisal of the actual number of eligible subjects that will be available and then actually entered needs to be conducted. This is obviously critical to powering your study and to its ultimate success.

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Many important large trials, well designed otherwise, have failed due to poor enrollment often at a huge expense for no definitive results.

Figure 4.1 simply depicts in a Venn diagram the process involved in predicting and then accruing the subjects enrolled in your trial. The outermost circle is the actual or perceived availability of patients in your clinic (or the clinics of multiple proposed sites in a multicenter trial) that might be approachable for screening. You need to base this initial estimate on data from your own practice and/or from national estimates. This number is important because it might speak to the potential impact your trial may ultimately have, but it does not accurately forecast your trial's enrollment. The next circle limits the potential subject pool to those that will meet at least the specific eligibility criteria you define for the trial. More on this below, but suffice to say this circle will be larger if the criteria are loose and will be much smaller if those criteria are more stringent. Moving inward, you then must be able to consent the subject to participate. This might seem like a forgone conclusion once you get this far, but many subjects, perfectly fit for trial inclusion otherwise, will simply not consent just because it is research, or due to other less predictable reasons. This process is well summarized by Lasagna's Law that states "*The incidence of patient availability sharply decreases when a clinical trial begins and returns to its original level as soon as the trial is completed.*" [1]. So, Muench's Third Law provides a ball-park conversion factor by stating "*In order to be realistic, the number of cases promised in any clinical study must be divided by a factor of at least 10.*" [2]. For our diagram, the final circle, colored in red, signifies the number of subjects ultimately consented and successfully enrolled in the study and is exactly 10% the size of the largest outer circle.

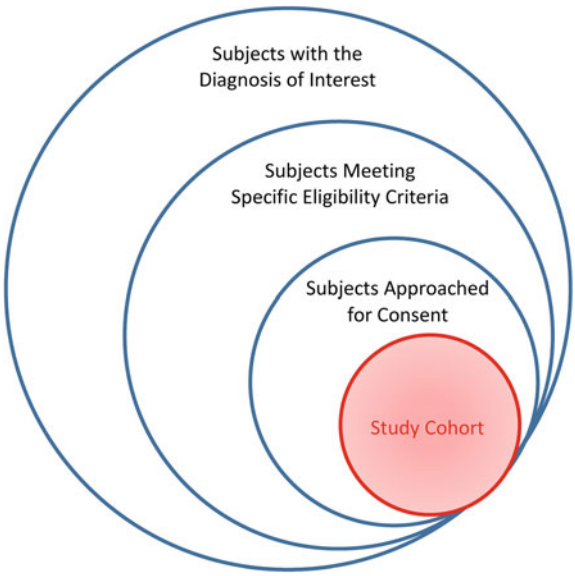

Fig. 4.1 Patient selection process

With this basic understanding, you now need to clearly define your target population. This is generally done by first identifying the disease process you are looking to study and then, within this cohort, refining the specific parameters of trial entry eligibility through clear inclusion and exclusion criteria. In general, these criteria will determine just how liberal or stringent enrollment will be for the trial. You'll need to decide how you want to approach this because it can be viewed as a "pay now or pay later" type of strategy. By using a more broad inclusive approach, you will be able to acquire a larger sample size that may generate more variance between subjects and will be more work and cost up front, but will likely offer definitive results at the end. If you opt for more specific, strict entry criteria, then you will end up with a smaller, better defined sample that may offer less "noise" and come with less effort and less cost, but you may then run the risk of not having power to achieve a definitive answer to your research question. This is yet another critical phase of trial planning.

Inclusion Criteria

Start by defining specific inclusion criteria to draw from the larger population of potential subjects with the diagnosis of interest. You can think of this as the "case definition" for the types of patients that are potential candidates for the trial. See Table 4.1 for common categories used for inclusion criteria. This process tends to be a little easier because you tend to know who you want to include, but be specific to be sure you define the target population precisely. The focus may be everyone with a certain disease process or potential eligibility for the intervention of interest, or it may be a specific degree of severity of disease or a specific diagnostic variant. Again, the broader the criteria the larger, but possibly more heterogenous, and the stricter the criteria the cleaner, but smaller, the starting sample.

In the selected clinical trials within the bibliography, the following list depicts the inclusion criteria defined in each trial:

Table 4.1 Inclusion Criteria

• Age range of subjects typical to the diagnosis of interest
• Gender
• Race/ethnicity
• Specific target population/subpopulation
• Diagnosis of interest
• Specific target disease stage, class or variant
• Specific risk factor or exposure of interest
• Index presentation of disease process (vs. recurrent/secondary treatment)
• Eligibility for proposed intervention
• Expected compliance with study protocol and all required follow-up

- Women with operable Stage I or II breast cancer and sufficient breast to allow a cosmetic result following tumor excision [3].
- Subjects under 75 years old with osteoarthritis of the knee and moderate pain despite non-operative treatment for 6 months [4].
- Men 18 years or older with a diagnosis of inguinal hernia [5].
- Subjects diagnosed with gastroesophageal reflux (GERD) by endoscopic or 24 h pH monitoring, or both, 12 months of symptoms requiring maintenance medical treatment, and equipoise regarding management [6].
- Subjects 18 years and older with an abdominal aortic aneurysm measuring ≥ 5 cm and meeting all approved instructions for use criteria for the aortic endograft [7].

In all cases, subjects had to be able to provide informed consent. Note that all these criteria are specific and fairly simple, but in some cases are more broad and inclusive, in other cases more focused and restrictive.

Exclusion Criteria

Setting specific exclusion criteria can prove more challenging. You may have to make some very difficult decisions here that will exclude potential subjects in whom you feel might benefit from the proposed intervention, but they present other confounding medical issues or logistical problems with your overall trial design. One such example might be morbid obesity. Unless this is your primary target population for intervention (i.e., bariatric procedures), then the obese subject, by being at generally higher risk for periprocedural complications compared to non-obese counterparts, may experience endpoints not directly relevant to your intervention. These may, however, be significant enough to create concerns over safety, to produce noise in the data, to present challenges with analyses, and to ultimately threaten definitive conclusions. Therefore, you might administratively choose to exclude morbidly obese subjects and consider a separate trial later in this population if warranted. This is the time to clearly identify known confounding disease processes or risk factors that will interfere with the study design and outcomes and eliminate them.

Consider that in a randomized trial, potential study candidates can be assigned to any of the treatments in the trial, whether it be the experimental treatment being evaluated or the control treatment. Therefore, exclusion criteria must consider the potential safety and contraindications to treatment for all treatments in the trial. For example, a trial might require general anesthesia for one of the surgical arms, but local anesthesia is sufficient for the other arm. However, the exclusion criteria will need to exclude people for whom it is not safe to give general anesthesia. These types of decisions may limit the eventual generalizability of your results. See Table 4.2 for common categories used for exclusion criteria.

Table 4.2 Exclusion criteria

• Age (i.e., often extremes of age)
• Gender
• Race/ethnicity
• Specific disease attributes (i.e., exclusion of advanced or end-stage disease)
• Confounding medical diagnoses
• Prior treatment of target disease process
• Prohibitive anatomic or physical characteristics
• Prohibitive medical risk
• Prohibitive risk for proposed intervention
• Limited life expectancy to achieve outcome or benefit
• Inability to consent
• Vulnerable populations
• Participation in other clinical trials

In the same referenced clinical trials, the following list depicts exclusion criteria defined in each trial:

- Women with Stage advanced III or IV breast cancer; tumor size >4 cm or adherence to the skin; inadequate breast size to allow tumor excision; fixed axillary or chest wall lymphadenopathy [3].
- Subjects with asymptomatic or minimally symptomatic osteoarthritis of the knee; less than 6 months of or inadequate medical therapy; prior arthroscopy within 2 years [4].
- Subjects in American Society of Anesthesiologists (ASA) class IV or class V; subjects with bowel obstruction, bowel strangulation, peritonitis, bowel perforation, local or systemic infection subjects with contraindications to pelvic laparoscopy; a history of previous repair with mesh; a life expectancy of less than two years; or subjects were participating in another trial [5].
- Subjects in ASA class III, IV, or V; morbid obesity (body-mass index (BMI) > 40 kg/m^2); Barrett's esophagus of more than 3 cm or with evidence of dysplasia; paraesophageal hernia; and esophageal stricture [6].
- Subjects with inadequate femoral artery anatomy based on anterior, >50% posterior, or circumferential artery calcification, aneurysm or pseudoaneurysm, or prior femoral artery surgery; prior clip based closure device; existing femoral infection or hematoma; renal insufficiency; life expectancy <1 year; allergy to device components; morbid obesity (BMI > 40 kg/m^2) [7].

As you can see, these are more detailed and cover in some cases a wide range of subject characteristics and risk factors for intervention. Although the inclusion criteria may offer enrollment to a potentially larger cohort of subjects, exclusions will often narrow the focus to those with more straightforward disease and minimal risk to intervention.

Vulnerable Populations

A word about vulnerable populations in clinical research. These represent specific categories of subjects that require additional protections to be in place prior to inclusion for enrollment. These include (1) pregnant women, (2) children, (3) fetuses and neonates, (4) subjects deemed decisionally impaired or mentally ill, (5) prisoners, and (6) students. Pregnant women and their fetuses require special protection because most medications and interventions have not specifically been tested in pregnancy. Also, you must consider the safety, risks, effects for both the mother and the fetus and so consent often requires both parents' agreement. Children require special protection because they are obviously not of legal consenting age. Safeguards should be in place since emotions run high between exposing children to risks versus the availability of what might be their only hope for treatment. Consent is obtained from the parents or legal guardians, but for children over the age of 12, their assent is also required. Prisoners require special precautions to avoid real or perceived advantages like improvements in living conditions or leniency for parole that might serve as enticement. The risks involved in the research must be the same as those for non-prisoner subjects, and selection should be fair for all eligible prisoners. Students require special precautions since they might view involvement as an enticement either for financial gain or for preference in school grading. The investigator(s) may be the students' teacher(s) and therefore in a position of authority which could affect the consent process. This extends to other situations where there is a hierarchical relationship between the investigator and the potential study subject, such as seen with medical residents and fellows. Mentally or decisionally impaired subjects may be the most frequently encountered vulnerable population and one of the more vexing. These individuals may satisfy all inclusion/exclusion criteria, but be unable to comprehend trial involvement let alone the detailed specifics of your trial. Consent must be signed by legal next of kin or guardian, or power of attorney. Again the risks associated must be the same as for those subjects able to consent themselves, and specific precautions need to be in place to address potential enticement, especially in terminal illness. Finally, although these potential subjects may be deemed incompetent to sign consent, they generally still retain the right to decline participation in research, especially if it offers no perceived benefit.

Informed Consent

The concept of informed consent takes on at least two important critical roles. An exhaustive discussion is beyond the scope of this chapter but, briefly, (1) the creation of a detailed informed consent document, and (2) the process of acquiring truly informed consent from the research subject. The required components and guidelines for creating an informed consent document are shown in Table 4.3.

Table 4.3 Informed consent

• Title of trial
• Investigator credentials and contact information
• Detailed description of subject involvement – Written at 8th Grade reading level – Avoid technical or complex terminology – Tailor to subject population
• List any benefits or potential benefits to the subject
• Detail risks and discomforts associated with participation – Define "more than minimal" risk – Statement regarding attempts to minimize risk – Coverage for treatment of study incurred injuries
• Compensation for subjects (if any)
• Confidentiality/data protection plan
• Availability/sharing of protected health information (PHI) – Health Insurance Portability and Accountability ACT (HIPAA) waiver
• Availability of future information, future use of data collected, or future contact for additional trial participation
• Any audio or visual recording of subjects, or use of subject's likeness
• National Institute of Health Certificate of Confidentiality (if applicable)
• Printed names and signatures – Subject – Subject's legal representative – Investigator providing/obtaining informed consent

It is advisable to use a template document that already includes all of these criteria and has been reviewed, vetted, and approved by your Institutional Review Board. This document can be reviewed during the consent process and then is signed by the subject or his/her legal representative if relevant, and by the investigator leading the discussion. A copy is provided to the subject for their records.

This brings us to the second component, acquiring consent. All too often this process is truncated or done at a superficial level, sometimes to avoid scaring the subject away. It is critical to allocate adequate time to spend with eligible research subjects in order to review the trial protocol in detail, explain the associated risks and benefits, and answer any and all questions they may have regarding their participation. This should be conducted objectively, transparently, and without bias. You are not trying to "talk them into" participating in the trial. In spending the necessary time, you are more likely to demonstrate your enthusiasm for the trial, to display confidence and competence to the subjects, and to garner their trust in you as the lead investigator. This is critical to minimize loss of subjects at this very last phase of the enrollment process.

"Practical Exercise"

As the last phase in planning our hypothetical claudication trial, let's see how we might define our study population and address enrollment and informed consent issues. We might start by hoping to enroll every single patent diagnosed with claudication, but given the discussion above we know that won't be feasible. Our inclusion criteria would start with clinically documented reproducible leg pain/fatigue with ambulation supported by noninvasive vascular studies showing a reduced ankle-brachial index (ABI) < 0.85 and/or a stress test demonstrating exercise induced leg ischemia and a further reduction in ABI by >15%. These definitions should adhere to accepted specialty society clinical practice guidelines. Next, we'd want to define exclusion criteria which might eliminate subjects with advanced peripheral arterial disease (PAD) and critical limb ischemia that might require more urgent revascularization, subjects with medical or physical limitations prohibiting their participation in any of the proposed supervised exercise protocols, subjects who have had prior intervention for their claudication, and subjects with alternative causes of their symptoms (i.e., neurogenic, musculoskeletal, etc.). We would limit the age range to the typical presentation of symptomatic PAD, say 50–80 years of age, and would exclude younger subjects whose atypical symptoms would likely be caused by a congenital or musculoskeletal etiology rather than PAD. Men and women would be equally eligible, but this would not be a disease of children or pregnant women. Specific provisions could be made for prisoners to participate if relevant. Finally, subjects would have to have a reasonable life expectancy, should be able to sign informed consent, and should be likely to be compliant with the study protocol. Control patients would meet similar inclusion/exclusion criteria, but would only receive counseling regarding smoking cessation and exercise and would be followed per standard medical practice. This later point might challenge the consent process because eligible subjects might prefer the availability of supervised exercise and not be agreeable to randomization to less supervised standard care. Alternatively, unwillingness to quit smoking or participate in any type of exercise, travel limitations, concerns over the safety and security of remote monitoring, and a bias toward intervention as an immediate definitive treatment over exercise and medical management may all further challenge our ability to gain consent. In the end, using our 10% rule, if we wanted to study 100 subjects as defined, we might need to anticipate screening upwards of 1000 patients who present with claudication—a potentially daunting task.

Summary

To this point, you have clearly and thoughtfully stated your research question and hypothesis, established primary and secondary endpoints for your outcomes, and have defined your intervention and control strategies. Now, you need to identify

and enroll the subjects into your trial to put this all to the test. You may feel all the heavy lifting is done in the prior three phases of design, but do not underestimate patient selection and enrollment. Set your inclusion and exclusion criteria so that you get the necessary balance between broad general inclusion and excessively stringent exclusion. This will hopefully provide you with the necessary number of subjects to power your study with reasonable effort and costs associated with the enrollment process, limited heterogeneity in the study groups with manageable variability in the resulting data, and ultimately the definitive answer to your originally proposed question.

References

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