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Conducting a successful clinical trial

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While the Randomized Clinical Trial (RCT) is one of many research designs, it is the most powerful design available to researchers for investigating the efficacy (i.e. producing the desired effect under very controlled, ideal conditions) and effectiveness (i.e. producing the desired effect under normal, practical conditions) of an intervention. Because the RCT is the design of choice whenever possible, but is also one of the most difficult designs to execute successfully, the following article offers tips gleaned from practical experience on several aspects of conducting a RCT. Some of the areas discussed are: often-overlooked aspects of writing a well-designed protocol, the importance of statistical consulting, strategies for good project personnel and subject management, the role of good public relations, developing a credible and useful budget, and strategies for improving record keeping and administrative efficiency. The article will be of particular interest to the principal investigator designing a RCT protocol and the project manager responsible for executing it.
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KEY WORDS: clinical trials, randomized clinical trials, organization and administration research support, research design, research personnel, research protocol, multi-centre study, chiropractic, manipulation.

L'essai clinique aléatoire n'est sans doute qu'un plan de recherche parmi tant d'autres; il s'agit néanmoins du plan le plus puissant à la disposition des chercheurs pour juger de l'efficacité d'une intervention, faite soit dans des conditions idéales et déterminées, soit dans des conditions normales et pratiques. Étant donné que l'essai clinique aléatoire est le plan préféré dans tous les cas où elle est utilisable, mais que son heureuse exécution est des plus difficiles, cet article offre des conseils, puisés à même l'expérience pratique, sur plusieurs aspects de cette approche. Les domaines étudiés englobent la façon (trop souvent oubliée) de rédiger un protocole bien conçu; l'importance de la consultation en matière de statistique; les stratégies en vue d'une bonne organisation du personnel et du sujet; le rôle de bonnes relations publiques; la formulation d'un budget crédible et utile; et les stratégies visant à perfectionner l'enregistrement des données et l'efficacité administrative. L'article intéressera tout particulièrement le chercheur principal rédigeant un protocole d'essai clinique aléatoire et le gestionnaire responsable de son exécution.
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MOTS CLÉS : essais cliniques, essais cliniques aléatoires, soutien organisationnel et administratif des recherches, plan de recherche, personnel de recherche, protocole de recherche, étude multicentres, chiropratique, manipulation.

Introduction

Conducting a successful clinical trial is a major undertaking. Several often heard euphemisms come to mind: *challenging, exciting, stimulating* . . . But the truth of the matter is, that even for the initiated, this type of research can also be fraught with unforeseen, frustrating problems. The reason for this is that if something can *possibly* go wrong, it probably will. The best of plans rarely unfold as expected and poorly planned and/or administrated projects inevitably fail altogether. Therefore, the purpose of this paper is to offer a few guidelines towards designing and executing a clinical trial.

A written protocol

The first, and perhaps most critical rule of conducting a successful clinical trial is to design the best research protocol possible. This will include putting to paper every detail, and all conceivable worst-case scenarios and contingency plans. While this may seem almost too basic to warrant special mention, it is not uncommon for people to undertake a project without ever writing *any* of it down. Some may feel that mental planning is quite adequate for the nature of certain projects; however, in this respect, conducting a study is similar to building a house: both require a written plan. Otherwise, the results are likely to be disastrous.

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TABLE 1
PUT TOGETHER A WRITTEN PROTOCOL

- do a thorough literature search and critical appraisal of the literature and check the literature for validity and reliability of your intended outcome measures
- plan for the worst case scenario
- hire a reputable statistician to consult on the research methods design and analytical tests
- do a sample size estimate, if possible
- while still designing the protocol, speak to the people you have in mind for the key personnel positions: are they interested in participating in the project, and how much remuneration would be attractive?
  (this will help you budget your payroll too)

The literature search

In designing a research protocol, the first task is to conduct a thorough search of the published literature on the topic. The literature should be examined for reliable and valid outcome measures which could potentially be used. It is important to take note of the strengths and weakness of these studies, so that good decisions can be made regarding which methodological features to incorporate and which to avoid in the study protocol.

A literature search can be conducted at most chiropractic college or university libraries – usually for a small fee. For anyone not having done an exhaustive literature search before, the college and university librarians are generally very helpful in explaining the procedure and providing the search service. Of course, once an inventory of relevant papers has been compiled, it is up to the investigator to critically appraise the papers for their strengths and weaknesses and overall usefulness in providing valid outcome measures and a rationale for the investigator's proposed study. For further information on critically appraising the literature, consult the seven-part series by Sackett et al.,[1–5] and the papers by Oxman et al.,[6] and Elenbaas et al.[7,8]

Statistical consultations

After completing the literature review, the next step is to consult with a good biostatistician. Several chiropractic colleges have statistical consultants on staff, and most universities offer statistical consulting services. Unless the investigator has acquired advanced knowledge in research design and biostatistics, this step is not merely an option, but a necessity. It is probably the single most important step one can take in developing a research design. Research techniques have advanced considerably in the last 20 years, so that a rudimentary knowledge of statistics no longer qualifies researchers to be their own statisticians. Admittedly, the biostatistican's fees may comprise a large part of the project budget, but a good statistician is worth the expense. The statistician can be instrumental in: (1) focusing the study's objective(s); (2) establishing the appropriate statistical test(s) for analyzing the data; (3) designing the methodology so that the data is analyzable; (4) designing the database; and (5) doing the data analysis.

It seems that the two most often used excuses by chiropractic researchers for *not* procuring statistical consultations are: (1) "I really don't think it's necessary to go to all *that* trouble . . . after all, I just want some results which will be directly meaningful to chiropractors." (2) "Statistics? Oh sure – looks like a pretty hokey science to me; you can prove anything you want with statistics." With regard to excuse number one, suffice to say that substandard research is regressive and unacceptable for any health care profession; while the excuse number two, one can only "prove *anything with statistics*" to an *ignorant* consumer of research who does not understand when certain statistical tests are appropriate and when they are not. While statistics is not a perfect science, properly used, it is a very important decision-making tool in the health sciences.

Selecting a good statistician is akin to selecting a good contractor: it is best to get referrals from respected researchers or to select consulting services (such as those offered by respected universities) based on their reputation. Telephoning the Research Department of a chiropractic college that is actively involved in reputable research would be a good place to start inquiries for referrals.

When calling the statistician to arrange an appointment, the investigator should have finetuned the study objective as much as possible, and should be sure to ask what other information to bring along. During the first consultation, the investigator should make the following inquiries:

1 What is the hourly fee rate, and how many hours will the statistician require to:

- do a Sample Size Estimation
- design a computerized database and demonstrate its use, and
- do the data analysis once the data has been entered into the database (by someone else who is cheaper)?

Statisticians are not inexpensive: one can expect to pay between $60–$100 (Canadian $) per hour; however, that should not be a deterrent, because the statistician *is indispensable*. Nevertheless, it is necessary to know the total amount to expect to pay for the statistician's consulting and analysis services, so that the budget can be adjusted accordingly.

2 Has the research question (objective) been stated properly?

3 Which statistical tests are most appropriate for:

- achieving the objective, and
- the nature(s) (nominal, ordinal, interval, ratio) of the data?

4 Is the RCT study design most appropriate? Is it feasible to use an RCT design, or do circumstances indicate a less powerful design such as a quasi-randomized controlled clinical trial, or a cohort trial?

The budget

The budget should not be assembled as an after-thought. Authors of research proposals tend to place mysterious dollar

TABLE 2
THE BUDGET

- try to include *every detail* in the budget (including such small items as paper clips, elastic bands, white-out, stamps, overhead acetates, copies of subject x-rays when subjects wish to take their x-rays to another doctor, publication reprints, snacks etc.)
- itemize the budget in detail, and document sources of the prices i.e. avoid mysterious, sweeping dollar figures

figures after broad, sweeping categories of expenses, and are then surprised when the funding agency grants them only a fraction of the requested amount. The way to minimize this is to itemize and document the pricing sources of every expense – including paper clips and elastic bands. As a result, the reviewers have a better understanding of what these "mysterious dollar figures" represent, and are hence more likely to approve the full amount of the budget request.

Administrative arrangements

If it is planned to conduct the trial in one or more institutional clinics or private clinics not belonging to any of the investigators, then an investigator and/or the Project Manager should meet with the clinic owner/chief administrator to arrange for official authorization to make the necessary demands of the clinic personnel. Subsequent periodic meetings with the owner/chief administrator and staff should also be considered, in order to promote a good working relationship and address any problems which may arise. While these steps may seem rather basic, they are frequently overlooked – particularly in academic settings where there is more than one outpatient clinic.

TABLE 3
ADMINISTRATIVE ARRANGEMENTS

- procure official (and preferably written) authorization to use any facilities and personnel which/who are not your own

Public relations

Once the statistician has been consulted and an appropriate research design has been established, careful consideration to the methodological details should be given. Such details play a major role in ensuring the success or failure of the project. One of the most important tasks involves incorporating strategies to secure the cooperation of *anyone* who is directly or indirectly involved with the study. This includes paid *and* unpaid personnel such as research assistants, the clinic administrative staff, the reception and radiology staff, clinicians, switchboard personnel, the comptroller, students . . . even the janitorial staff.

TABLE 4
PUBLIC RELATIONS

- inform *everyone* in the clinic about the project (when, where, why, who is involved) through personal contact, posters, periodic bulletins – and *keep* them informed (how many subjects are enrolled to date, status and project)
- budget honorariums for clinic staff who are not formally *project staff*, but whose cooperation is essential to the smooth-running of the project

Without the goodwill and cooperation of any one of these people, serious complications may ensue. It is important to meet privately with each person involved to outline the protocol; this includes verbally explaining and presenting *in writing* the role this person will play, as well as the corresponding remuneration.

If possible, the investigator should try to budget token honorariums for all those who will not be *formally* employed by the project, but whose cooperation is important to the smooth progression of the project. The success of the project for example, may depend, to some extent, on the alertness and goodwill of perhaps the x-ray technicians, the clinic receptionists, or telephone switchboard staff, to recognize and refer qualifying subjects to the study.

If the study will be conducted in an institutional or larger-clinical setting, positive Public Relations informing everyone about the progress of the study is helpful in maintaining a feeling of goodwill and enthusiasm towards the project. One means of achieving this is to prominently post (where permitted) graphic "Subject Thermometers" illustrating how many subjects the study has processed to-date.

As mentioned above, the success of the project will depend to some extent upon the cooperation and goodwill of some of the staff – and possibly students – of the institution/clinic to accomplish certain critical stages of the project. Therefore, it is essential to not only inform these players about the study, but also for the investigators and project manager to take every opportunity to praise and thank them for their help. While monetary compensation can be a very effective motivating tool, it cannot compensate for unpleasant working conditions. It is important to maintain good morale among all participants, including the subjects being studied. Frequent verbal expressions of appreciation from the investigators and project manager are effective morale-boosters, as are occasional project-funded dinner/breakfast/wine-and-cheese get-togethers for all the research personnel. This latter strategy works very well, but must of course, be budgeted for.

Should the study take place in a chiropractic college setting and be relying on student cooperation in some way, then it is essential to obtain permission from certain class professors in order to make one or two announcements in class about the student's roles in the project.

Personnel management

An important part of the grant application (proposal) budget is the *payroll budget*. It cannot be over-emphasized that it is *not* an area to start economizing. Realizing that good personnel are hard to find – and keep – investigators and project managers should endeavour to make working conditions as pleasant as possible, and offer competitive fees and salaries. Otherwise, the project manager will likely have to contend with a high personnel turnover rate, whereby a lot of time and energy will be expended rehiring and retraining people, only to see them leave as soon as more lucrative opportunities arise.

However, refrain from putting part-time personnel on *salary*. Instead, use a *time-sheet system* whereby the part-time assistants are paid for the actual number of hours they work. This way one not only avoids overpaying people when the project experiences some unexpected slow-periods, but the frustrations of repeatedly putting people on and pulling them off the payroll during any unanticipated personnel turnovers are also avoided.

A potentially serious problem may arise if the protocol does not include a detailed job description for *everyone* who plays a role in the project. Each player should receive a copy of his/her own job description in order to minimize misunderstandings regarding the incumbent's responsibilities and remuneration. This measure will minimize not only misunderstandings, but also potentially ensuing inefficiencies, costly errors, and strained goodwill. It will also help prevent possible legal actions by staff members who may feel that the terms of the hiring agreement were not met.

Further, not only is it advisable for the principal investigator(s) and project manager to meet individually with each research assistant before the project commences, it is also advisable to rehearse the incumbent's role with him/her. For example, if one of the research assistants has the responsibility of delivering an orientation speech and obtaining consent from prospective subjects, it should be part of the protocol that a principal investigator or the project manager practices the speech with the research assistant prior to any contact with subjects. This will help ensure a professional demeanour with all subjects.

When developing job descriptions, another consideration is the relationship between the Principal Investigator and the Project Manager. The Principal Investigator frequently devotes only part of his/her time to a project; therefore a serious clinical trial will require the services of a full-time Project Manager. Having a Project Manager, no matter how capable this person is, does not absolve a Principal Investigator from being fully aware of the status of the project at any given time, or of being available to the Project Manager for consultation. It is recommended that a provision be made for the Project Manager and the Principal Investigator to have a short conference once every working day – either in person or over the telephone – to assess the day's activities and address any problems. The Project Manager, in turn, should briefly check with all project personnel about once *every working day*. In addition, the Project Manager should be readily accessible to everyone involved in the project.

TABLE 5
PERSONNEL

- speak privately with anybody who will directly or indirectly be involved in the study
- rehearse the roles of all project personnel
- give each project personnel member his/her own written job description
- the Principal Investigator should be readily available to the Project Manager
- make sure the Project Manager is readily available to the project staff
- the Principal Investigator should meet/speak with the Project Manager at least once every day
- the Project Manager should meet/speak with all project personnel at least once every day
- do your best to *keep* good personnel: offer attractive remuneration, acknowledge and praise work well done, try to make working conditions as pleasant as possible
- use time-sheets for part-time personnel

Subject management

If the study protocol should involve assessing and treating subjects by appointment, then it would be prudent to ensure that one of the research assistants' job description includes setting aside some time each evening to make "reminder telephone calls" to subjects having appointments the following day. This provision will contribute greatly towards maximizing subject compliance and minimizing the inconveniences associated with rebooking "no-shows".

Another simple measure which can contribute significantly to the efficiency of project proceedings is the acquisition of a telephone answering machine. An answering machine is particularly useful when subjects are required to telephone in response to a recruitment advertisement. When one considers the cost of hiring a full-time person to answer the telephone, or the potential problems of placing an additional burden on the in-house

TABLE 6
SUBJECT MANAGEMENT

- install an answering machine to facilitate the subjects' communications with the project staff
- telephone all subjects the evening before the day of their appointment to remind them of their appointment
- ensure that all project personnel are friendly and courteous to all subjects – no matter how trying a subject may be

switchboard staff, an answering machine is often a very good and economical alternative investment.

Be organized

To successfully conduct a research project, everything must be properly organized. To this end, it is particularly useful for each project member to have a "*Do List*" for every working calendar day. The Project Manager should set aside time every evening or afternoon to complete each member's (including his or her own) "*Do List*" of prioritized tasks for the following day. Relevant tasks should be added to the appropriate "*Do List*" **immediately** after they come to the Project Manager's attention. For this system to work, everyone must consult their *Do List* frequently and routinely throughout the course of a day and must execute the task without undue delay. Whatever does not get done on a particular list, is then carried over to the next day's list. Properly implemented, this system greatly improves the chances of non-routine tasks being executed in a timely fashion.

TABLE 7
BE ORGANIZED

- finish drafting a daily DO LIST for all project personnel every evening for the next day, and prioritize the tasks
- add tasks to the appropriate DO LIST as soon as they come to mind (do not think you will remember to do it later)
- don't save for tomorrow what can be done today

Record-keeping

A very important but often neglected area of administrating a project is that of record-keeping. Most protocols make some effort to describe a record-keeping system, but few provide well defined details regarding: (a) exactly how the paperwork will be processed and filed so as to maximize the efficiency of subject flow, *and* be readily retrievable; (b) how the data will be processed and prepared for analysis; and (c) how the expenditures and the financial records will be managed and reported.

An efficient and desirable record-keeping system should be designed in such a way that if need be, just about anyone could understand and use the system with little or no prior explanation. Generally, this means that: (1) every file folder, every floppy disk, every box, every x-ray, *everything*, be properly labelled; (2) every expense be recorded in a properly labelled ledger book or spreadsheet program; (3) the paperwork be filed in logical categories and alphabetically; and (4) all records and data be kept together in a centralized area. In case of theft, fire or some other disaster, it would be wise to store one or two duplicate sets of important documents, floppy disks and/or written data records at another location.

The Project Manager should also ensure that the data are entered into the electronic database *exactly* as prescribed by the statistician. In addition, the data should ideally be entered with frequent regularity, rather than all at once at the end of the data-gathering phase. With respect to data-entry, it would be much more cost-effective to assign this task to someone hired for this purpose, rather than to the statistician.

TABLE 8
RECORD-KEEPING

- try to record data as it comes in rather than all at once at the end
- make duplicates of all your data and store them away from the originals
- keep track of all expenditures, even if there is an accounting department doing the same
- label ALL records, files, envelopes, disks, folders, binders, boxes etc. *properly*, and store all records systematically and logically, so that virtually *anyone*, (if, for example the project manager should be away for some reason) with a minimum of briefing, could understand the system and find any required record/document

Conclusion

A comprehensive summary of all the aspects of conducting a clinical trial discussed in this paper is summarized in Table 9. The points discussed in this paper are by no means exhaustive; however, an attempt has been made to address some of the most neglected areas of conducting a clinical trial – areas which can ultimately "make or break" a project. While a useful outcome for any clinical trial cannot be guaranteed, affording these areas due consideration can certainly improve the chances of success.

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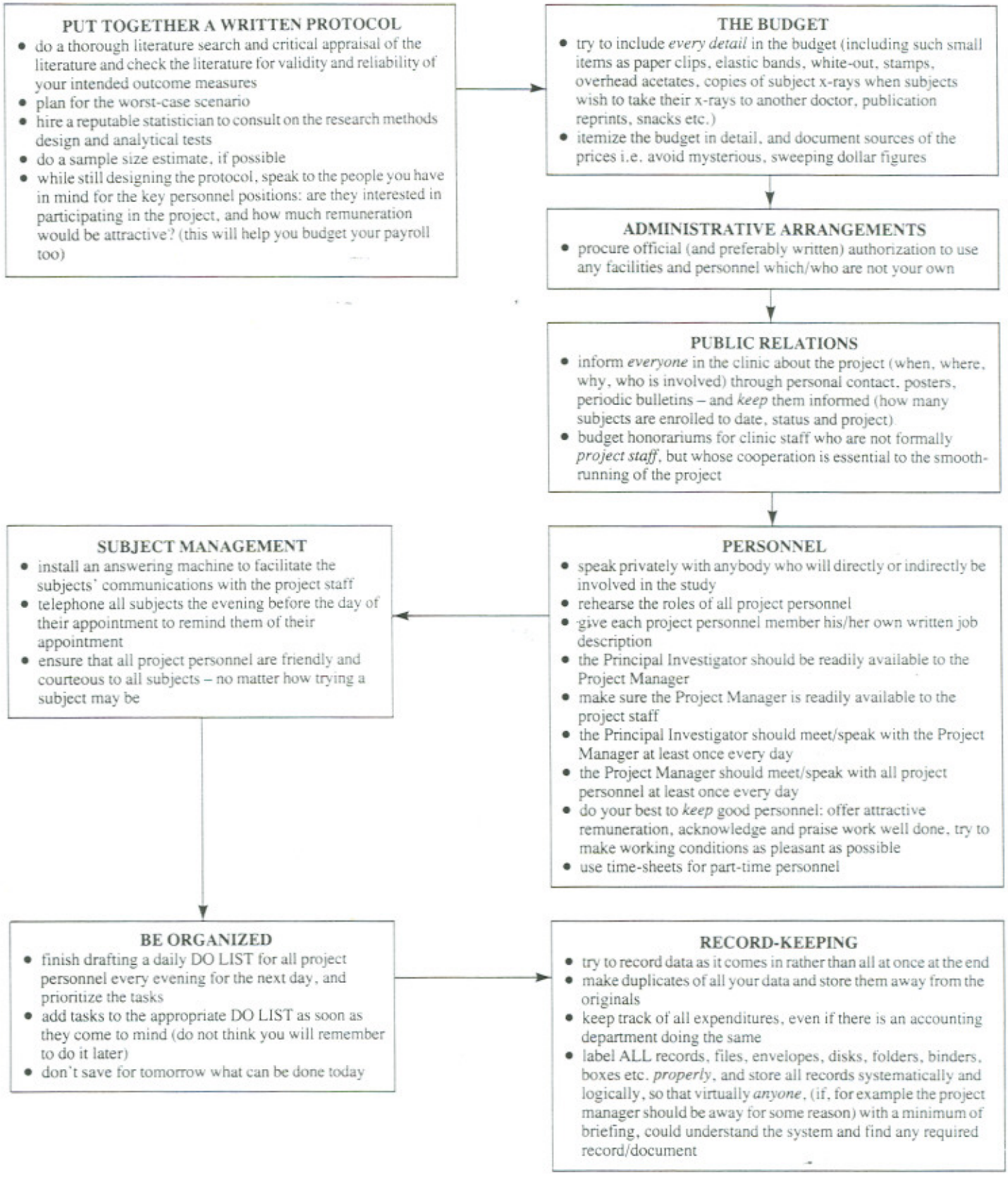
TABLE 9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