# مقدمات کارآزمائی بالینی

# موضوعات مورد بحث

- انتخاب بیماران و کنترل ها
- پی گیری
- نکات اخلاقی
- کارآزمائی بالینی متقاطع

# انتخاب بیماران و کنترل ها

## نیاز به منشور

منشور سندي است که طرح پژوهش را تعیین می کند.

سخت ترین بخشها در یک منشور عبارتند از:

طرح و توسعه یک مساله عملی-علمی با ارزش است.

اطمینان از وجود و کفایت زمان، بودجه و ... براي پاسخ به مساله پژوهشی

پیش نویس منشور مطالعه، یک مرحله ابتدایی مفید در توسعه آن است. این شامل سندي یک یا دو صفحه اي است که خصوصیات علمی و بالینی طرح را توصیف می کند. در کنار این که کمک می کند سند نهایی را شکل دهد، می تواند جنبه علمی طرح را عرضه و نظر دیگران را راجع به آن بسنجد.

بسیار لازم است که وفاداري شدیدي به منشور وجود داشته باشد. به این ترتیب و با به کار گیري یک منشور دقیق، حداقل تفسیرهاي شخصی وارد مطالعه خواهد شد

منشور ها کاربردهاي زيادي دارند:

تنها و مهم ترین ابزار سنجش کیفیت مطالعه، منشور آن است زیرا:

۱. شامل شرح دقیقی از درمان و روش درمان است.
۲. تنها و موثرترین راه به اشتراك و داوري گذاشتن ایده و روش پژوهشگر به صورت دقیق با دیگر پژوهشگران است.
۳. براي بسیاري از پژوهشگاه ها و مراکز، منشور یک مبناي انجام پژوهش است و از اهمیت بالایی برخوردار است.
۴. نتیجه هاي کمی پژوهش براساس طرح تحلیل داده ها که در منشورمشخص شده حاصل خواهند شد. بنابراین تمام جنبه هاي آماري مطالعه در منشور بیان شده اند.
۵. منشور و فرم رضایت نامه همراه آن مرجع رسیدگی به وضعیت رعایت مسایل پزشکی و اخلاقی طرح است

سرفصل هاي عمده در منشور مطالعه:

زمینه ها و هدف کلی و اهداف ویژه
معیارهاي ورود/ خروج بیمار
روشو نحوه دقیق انجام درمان
پاسخ بیمار و روش ارزشیابی آن
نوع کارآزمائی و چرایی انتخاب آن ( شاهددار تصادفی شده و ...)
نحوه بیماران به گروه هاي درمانی
مسایل اخلاقی و اجازه آگاهانه بیمار
نوع طرح و تحلیل آماري و اندازه نمونه لازم
نحوه کنترل و پایش کارآزمائی
پیش بینی نحوه برخورد با آن - انحراف از منشور مطالعه و ...

منشور مطالعه

سه پرسش مهم در طرح کارآزمائی بالینی:

بیمار واجد شرایط کیست؟

درمان ها کدامند؟

چگونه نتیجه درمان ارزشیابی شود؟

دو وظیفه عمده منشور مطالعه عبارت است از:

طرح عملی: از ورود تا خروج یک بیمار را تشریح و وظایف افراد مختلف را در قبال هریک مشخص نماید.

شرایط ورود/خروج

درمان و ارزشیابی

و ...

طرح علمی:

شرح و بیان مساله

اهداف کلی کارآزمائی بالینی

و ...

## انحراف از منشور مطالعه

برخلاف اهمیت منشور مطالعه، جزییات بیان شده در پروتکل ممکن است تا حدودي براي هر بيمار متفاوت باشد. مثلا
هرفرد تفسیر خود را از منشور داشته باشد.

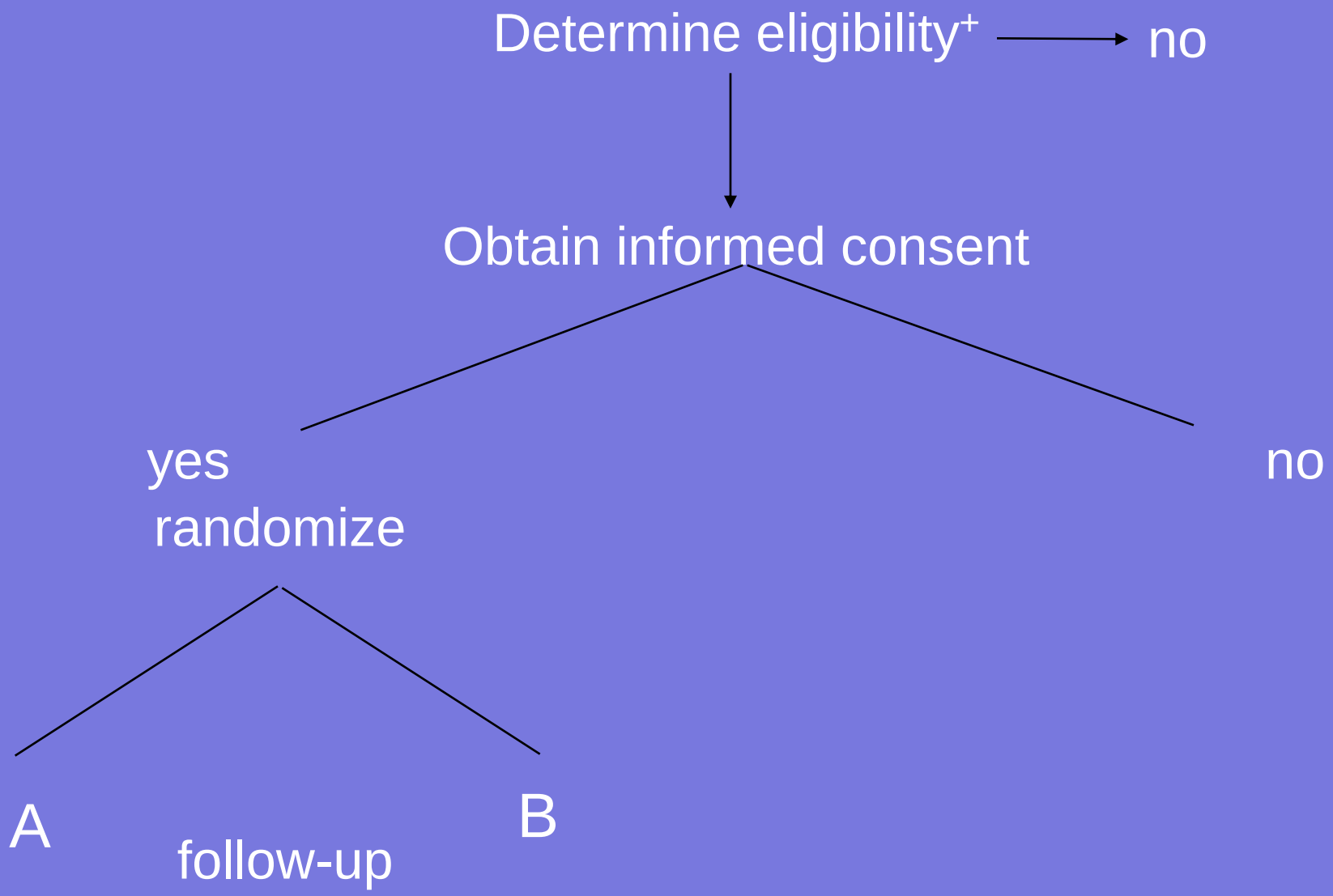
اغلب انحراف از منشور مطالعه ناشی از رخ داد حوادث پیش بینی نشده در منشور مطالعه است که منجر به تفسیر شخصی در انتخاب بهترین درمان می شود.

# Steps in Patient Registration (Randomization)

1. Patient requires treatment
2. Patient eligible for inclusion in trial
3. Clinician willing to randomize patient
4. Patient is willing to be randomized (consent is obtained)
5. Patient formally entered in trial
   - Treatment assignment obtained from randomization list
   - Case-report completed
6. Treatment begins

# Usual Sequence of Events in a Randomized Clinical Trial

[+] In many trials consent must also be obtained for screening.



# Key Elements of Informed Consent

- A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental
- A description of any participant discomforts and risks reasonably to be expected
- A description of any benefits to the subject or to others which may be expected
- A disclosure of any appropriate alternative procedures that might be advantageous for the subject

# Key Elements of Informed Consent (cont.)

- An offer to answer any inquiries concerning the procedures
- Instructions to a subject concerning the freedom to withdraw his/her consent and to discontinue participation in the project or activity at any time without prejudice or explanation
- Reasons study may be stopped

# Key Elements of Informed Consent (cont.)

- An explanation as to whether compensation and medical treatment are available if physical injury occurs and, if so, what it consists of or where further information may be obtained
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained

# Informed Consent (cont.)

- Length of sample informed consents:
  - ESPRIT (8 pages) (experimental treatment:IL2 and AIDS therapy)
  - SMART (12 pages) (treatment strategy trial using approved drugs)
  - START (14 pages) (treatment strategy trial using approved drugs)
  - MRFIT (Multiple Risk Factor Intervention Trial): 1 page
- Strategies for Management of AntiRetroviral Therapy (SMART) Study

# Informed Consent (cont.)

- Comprehension (when assessed) by participants is low on key items suggesting simpler, not longer, forms may be better.
- Separate consent documents for stored specimens and substudies
- Multiple reviews of consent: Institutional Review Board (IRB), Ethics Committee and sponsor

Attach ID Label Here

□-□□□□□□-□□□□

Write Participant ID Here

6 16

Today's Date: MONTH □□ DAY □□ YEAR □□

## CONSENT FOR PARTICIPATION IN STUDY

I understand that the tests I have had thus far suggest that my risk for a heart attack is considerably above average.

I understand that the program is planned to be of six years' duration and that all participants in the program will be expected to attend the clinic for a free periodic physical examination including blood pressure measurements, electrocardiograms, an exercise test, blood tests related to heart disease, and questions regarding diet and smoking habits. I understand the program will not be a substitute for usual medical care.

I understand that all men in the Program will be carefully studied and observed for six years. The men who agree to participate in the Program will be allocated randomly into one of two groups. Approximately half of the participants will be referred to their regular source of medical care for treatment and advice relating to the factors which place them at a higher than average risk of a heart attack; but also they will be invited to return periodically to have without charge, a physical examination and laboratory tests.

The remaining half of the participants will be offered an ongoing series of specific preventive measures including intensive efforts to modify behavior with respect to diet and smoking. These intervention efforts will be performed using standard counseling techniques in both individual and group settings. If a participant's blood pressure is elevated, a Program physician may decide that it is important to treat it with medicine; I understand that individuals occasionally experience side effects from these medicines, such as rashes or upset stomach. Physicians and nurses will watch closely for these side effects and when necessary, stop the medicine.

I understand to my satisfaction the program of study and the procedures which will be performed. I have had an adequate chance to ask questions and I may ask further questions at any time while the study is in progress.

I understand that I am free to withdraw my consent and discontinue my participation in the study at any time. I also understand my continuing participation is important to the success of this national prevention program.

This is to certify that I, _____, agree to participate in the Heart Attack Prevention Program.

1 □ CC USE

_____ Date

_____ Signature of Participant

1 □ CC USE

_____ Signature of Auditor/Witness

1 □ CC USE

# Participants

- Inclusion criteria to maximize:
  - rate of outcomes (old, weak)
  - likely benefit from intervention (renal disease, institutionalized, vitamin D deficiency)
  - generalizability
  - ease of recruitment

# Exclusion Criteria

- Intervention unsafe
- Intervention unlikely to be effective
- Unlikely to join to the intervention
- Unlikely to complete follow-up
- Practical problems

# Choice of Intervention

- Maximize
  - effectiveness *(highest tolerable dose)*
  - safety *(lowest effective dose)*
  - generalizability
  - trial design/conduct
    - recruitment
    - compliance
    - blinding

# Choice of Control

- Inert placebo usually best, but might not be possible (ethic considerations)
- Active therapy for control =

  equivalence trial:
  - Ho: not more than a stated difference between groups
  - Ha: one treatment better

# Participation in Clinical Trials

## Why Some Participate:

- Give back to society
- Exhausted all other txs
- Health care services
- Payment & incentives
- Support
- Others??

## Why Some Do Not?

- Mistrust of studies
- Do not want to be “guinea pig”
- Do not meet criteria
- Cannot give up time for study visits
- Barriers: distance

# Taking Part in Research Studies: Questions to Ask

- What is study about?
- What are the goals?
- Study sponsor?
- Participant input into protocols?
- Inclusion criteria?
- Benefits & risks
- Is there an incentive?
- How protected from harm?
- What is required: # study visit & what occurs?
- What happens after study is over?
- How results will be disseminated?

# Follow-up

RQ: Does diet and exercise reduce risk of developing type 2 diabetes in persons with glucose intolerance?

Design: Randomized trial

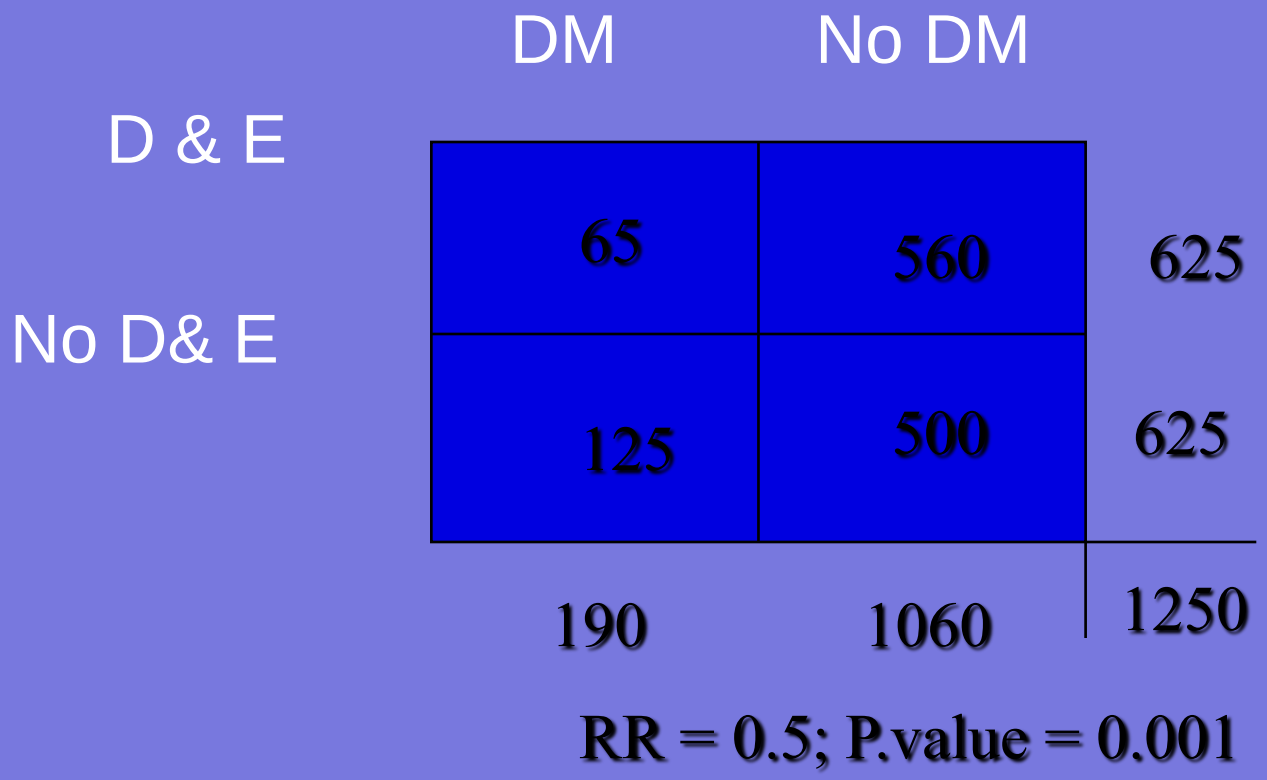
Subjects: 2500 with glucose intolerance

Intervention: low fat weight loss diet and moderate intensity aerobic exercise

Measurements: Predictor = treatment

outcome = development of diabetes

# Diet and Exercise to Prevent Diabetes in Persons with Glucose Intolerance




RR = 0.5; P.value = 0.001

# Maximizing Adherence and Follow-up

- Choose subjects likely to adhere
  - exclude if likely nonadherent
  - complete several visits before randomization
  - complete a run-in
- Intervention easy and safe
- Visits easy and enjoyable
  - frequent enough to be engaging
  - night visits, travel and parking reimbursement
  - personal relationships with participants
- Measurements easy, safe and painless

# Outcomes in Clinical Trials

- Efficacy Outcomes
  - Primary
  - Secondary
  - Surrogate
  - Composite
- Adverse Effects
  - rare
  - common

# Raloxifene Use for the Heart

- Potential Outcomes
  - Mortality
  - CHD events (death, MI)
  - Stroke
  - Breast cancer
  - Fracture
  - LDL-cholesterol
  - Quality of life

## How to Proceed?

- Measure all outcomes
- Pick one primary outcome
  - estimate sample size
- Make all the rest secondary

# Adverse Events and Side Effects

- Anticipated
  - use specific questions
- Unanticipated
  - ask about general adverse experiences
- Rare
  - sample size inadequate
- Common
  - multiple differences between groups

# High Quality Randomized Trials

- Eligibility ( Inc & exclusion) Generalizability
- Blind randomization ( Concealment)
- Blinding of participants, study staff, lab staff, outcome ascertainment and Judgment
- Join to study intervention
- Complete follow-up
- Adequate power
- Statistic and interpretation
- etc

# نکات اخلاقی

# Ethical Considerations

- Major issue for ‘Randomized Controlled Trial’
- Proper information to all the study subjects
- Informed consent
- The trial is conducted ethically
- Avoid bias in results
- Sample size is adequate to give the results
- What if, before the study is completed, there is evidence that one treatment is better than the other one

# ETHICS

## IMPORTANT ISSUE IN CLINICAL TRIALS

## ETHICAL CLEARANCE

* INSTITUTIONAL REVIEW BOARDS (IRBs)
* ETHICAL COMMITTEES
* …

# ETHICAL ISSUES IN RANDOMIZED TRIALS

1. Concept of *equipoise* (تعادل)- the point at which you are not sure whether the placebo is better or the treatment is better. This is the point at which a trial is best started.

2. The more information accumulates on a new treatment, the harder it is to do a trial

3. It can be unethical to deny a new treatment to the placebo group, but the history of trials suggests that it is often better to be in the placebo arm.

Example:

In neonates - sulfa for infections, oxygen for lung disease, steroids for eye disease were all damaging, and this was discovered only via randomized trials

4. It can be unethical *not to perform* a trial, because it prevents new knowledge from being obtained and used.

Example:

Folate for neural tube defects

5. Public health is always best served by proper evaluation, and the best evaluation is by randomized trial.

# کارآزمائی بالینی متقاطع

# CROSS-OVER

**The problem that the control arm may get the treatment from other sources. Common problem in screening trials.**

# Special Trials: Cross-over Trial

- Usually for chronic disease (why?)
- Randomize to whether receive treatment first or control first
- Wash-out period for each subject between periods
- Dropouts a problem