5th ECReCo
Aix en Provence, August 29-31, 2015

Plenary 5

Organising a study

Linos Vandekerckhove and Alison Rodger

Outline of Session

- Developing the research question/s
- Writing the grant application/ study protocol
- Conducting the study

Funding sources to get started

Defining the goal/objectives you want to achieve

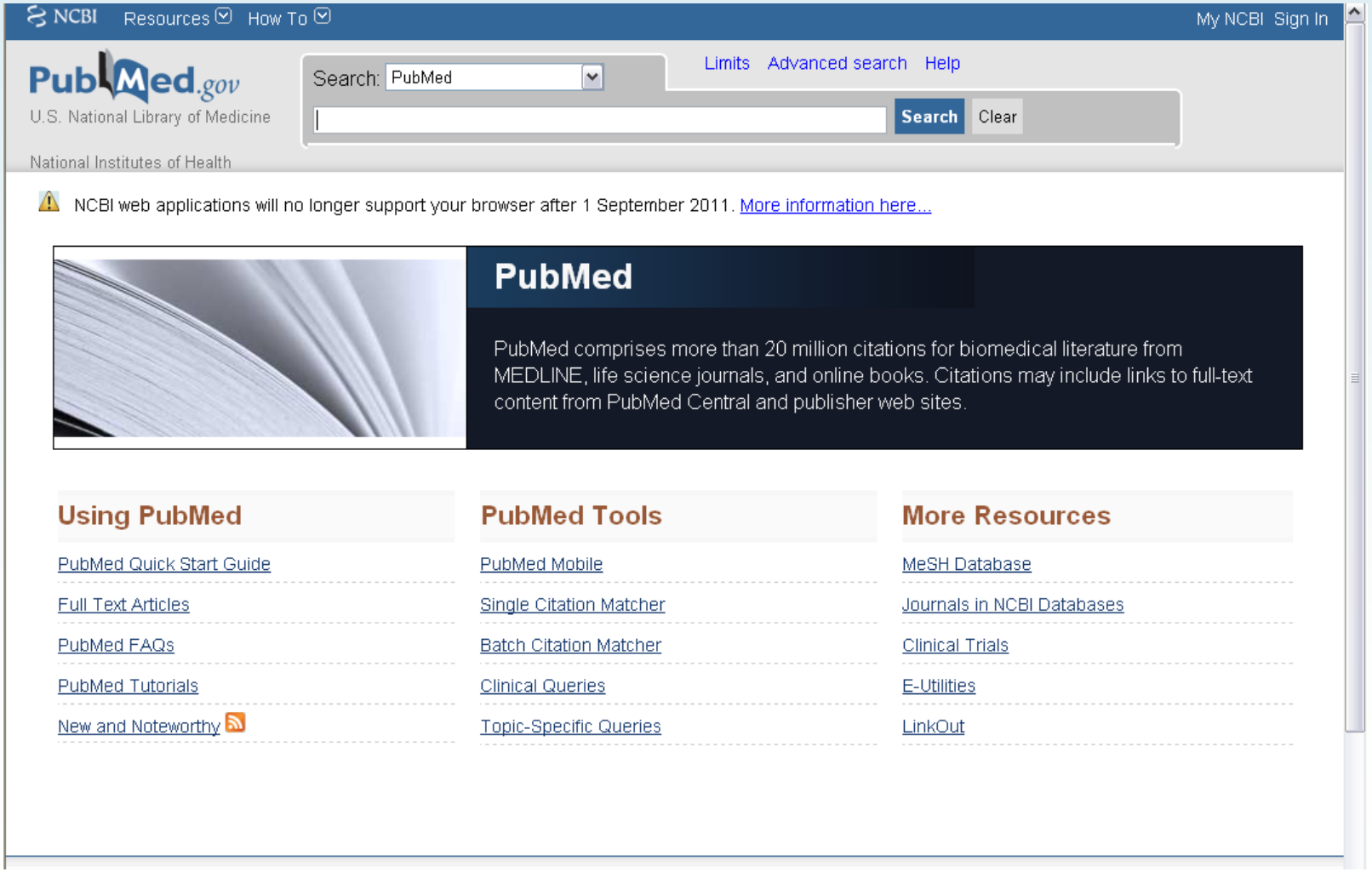
- **S**pecific: is the objective clear
- **M**easurable: are there clear indicators or parameters
- **A**cceptable: do the objectives provide an acceptable solution to the problem?
- **R**ealistic: is the objective achievable
- **T**imely: when will the objective be achieved?

Clinical trials:From a good idea to the implementation of a clinical trial

- A good idea
- Literature and web search
- Writing the protocol
- Inclusion and exclusion criteria
- Calculation of the sample size
- Feasability assessment
- Administration
- Ethical conduct Safety
- Economics
- Participating in a clinical trial
- Information technology
- Controversy

A good idea

Literature and web search



Writing a protocol

TABLE OF CONTENTS

Goal of the study:

- Primary objective: to evaluate the safety of …
- Secondary objectives:
  - Inflammation
  - Immunologic endpoints
  -

Inclusion criteria: some examples

- 1. Male or female, aged 18-60 years
- 2. Confirmed HIV-1 seropositive documented in the past 6 months (by acute antiretroviral syndrome, p24 antigenemia and/or ELISA seroconversion)
- 3. Willing and able to give written informed consent for participation in the study
- 4. Willing and able to adhere to an effective HAART regimen for the duration of the study
- 5. CD4 cell count > 350 cells/ml at screening and at the preceding clinic visit
- 6. No new AIDS-defining diagnosis or progression of HIV-related disease.
- 7. Haematological and biochemical laboratory parameters as follows:
  - 1. Haemoglobin > 10g/dl
  - 2. Platelets < 100,000/dl
  - 3. ALT ≤ 2.5 x ULN
  - 4. Creatinine ≤ 1.3 x ULN

Exclusion criteria

- 1. Confirmed HIV-2 seropositive
- 2. Positive pregnancy test
- 3. Presence of NRTI mutation in the screening genotype
- 4. Participation in another clinical trial within 12 weeks of study entry
- 5. History of autoimmune disease other than HIV-related auto-immune disease.
- 6. History or clinical manifestations of any physical or psychiatric disorder which could impair the subject‟s ability to complete the study
- 7. History of anaphylaxis or severe adverse reaction to vaccines
- 8. Previous immunisation with any experimental immunogens

SUBJECT WITHDRAWAL CRITERIA

- 1) Each participant has the right to withdraw from the study at any time. Any individual for who is being considered for discontinuation or postponement of treatment will be discussed with the trial team.

- 2)Significant non-compliance with treatment regimen or study requirements.

- 3) A very severe local or systemic reactogenicity event judged to be possibly, probably or definitely related to the study intervention.

- 4) A very severe or serious adverse event judged to be possibly, probably or definitely related to the study intervention.

STUDY PROCEDURES: INFORMED CONSENT

- The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

STUDY PROCEDURES: INFORMED CONSENT

- Written and verbal versions of the Participant Information Sheet and Informed Consent should be presented to the participants explaining:
  - the exact nature of the study
  - the implications and constraints of the protocol
  - the known side effects and any risks involved in taking part

- It should be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

- Local site investigators
  - A physician's first duty is to guarantee safety to his/her patients, and if a physician investigator believes that the study treatment may be harming subjects in the study, the investigator can stop participating at any time.
  - The local investigators are responsible for conducting the study according to the study protocol, and supervising the study staff throughout the duration of the study.
  - The local investigator or his/her study staff are responsible for ensuring that potential subjects in the study understand the risks and potential benefits of participating in the study; in other words, that they (or their legally authorized representatives) give truly informed consent.
  - The local investigators are responsible for reviewing all adverse event reports sent by the sponsor.
  - The local investigators are responsible for making an independent judgment of these reports, and promptly informing the local monitoring board of all serious and study-treatment-related adverse events.

PROCEDURES FOR RECORDING ADVERSE EVENTS

- The following information will be recorded:
  - description
  - date of onset and end date
  - severity, assessment of relatedness to study medication
  - other suspect drug or device and action taken
  - Follow-up information should be provided as necessary

RANDOMIZATION AND CODEBREAKING

- Randomization
- Codebreaking:
  - The blinded treatment assignments will be accessible to the investigator if a subject need to be unblinded in an emergency using the unblinding envelopes provided to the ...
  - If unblinding occurs, the investigator or study pharmacist must record the reason for unblinding, as well as the date and time of the event.
  - Corresponding information will be recorded on the CRF by the investigator.

STATISTICAL METHODS AND SAMPLE SIZE

- **STATISTICAL ANALYSIS**
- **SAMPLE SIZE CALCULATION**
- **INTERIM ANALYSES AND STOPPING RULES**

QUALITY CONTROL AND QUALITY ASSURANCE

- Perform regular monitoring according to ICH-GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.
- Monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable and local regulatory requirements.

  - Review the CRF data
  - Provide instructions and training to the sites involved in the trial.
  - Detail of any other steps taken to ensure quality of research.

Ethical Conduct

- Clinical trials are closely supervised by appropriate regulatory authorities. All studies that involve a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial.

- To be ethical, researchers must obtain the full informed consent of participating human subjects.

- Informed consent is clearly a necessary condition for ethical conduct but does not ensure ethical conduct. The final objective is to serve the community of patients or future patients in a best-possible and most responsible way.

Administration

- Clinical trials designed by a local investigator and funded clinical trials are almost always administered by the researcher who designed the study (and applied for the grant) (Eudract number).
- Phase III and Phase IV clinical trials of new drugs are usually administered by a contract research organization (CRO) hired by the sponsoring company.
- At a participating site, one or more research assistants (often nurses) do most of the work in conducting the clinical trial.

DATA HANDLING AND RECORD KEEPING

- Data will be collected by the site personnel and recorded on the CRFs (case report form's).

- Other source documents include but are not limited to:
  - Documentation of any existing conditions or past conditions relevant to eligibility
  - Signed Informed Consent Forms
  - Reported laboratory results

- A file will be held at the trial site for each patient containing all the CRFs and source documents. All essential documents will be kept in a secure location and retained as required by ICH-GCP and applicable local requirements.

Economics

- Investigators
  - Many clinical trials do not involve any money. However, when the sponsor is a private company or a national health agency, investigators are almost always paid to participate

- Patients
  - In Phase I drug trials, participants are paid because they give up their time (sometimes away from their homes) and are exposed to unknown risks, without the expectation of any benefit. In most other trials, however, patients are not paid, in order to ensure that their motivation for participating is the hope of getting better or contributing to medical knowledge, without their judgment being skewed by financial considerations. However, they are often given small payments for study-related expenses like travel or as compensation for their time in providing follow-up information about their health after they are discharged from medical care

Information Technology

- The last decade has seen a proliferation of information technology use in the planning and conduct of clinical trials.
- Clinical trial management systems (CTMS) are often used by research sponsors or CROs to help plan and manage the operational aspects of a clinical trial, particularly with respect to investigational sites.
- Web-based electronic data capture (EDC) and clinical data management systems (CDMS) are used in a majority of clinical trials to collect case report data from sites, manage its quality and prepare it for analysis.
- Interactive voice response systems (IVRS) are used by sites to register the enrollment of patients using a phone and to allocate patients to a particular treatment arm.
- Patient-reported outcome measures are being increasingly collected using hand-held, sometimes wireless ePRO (or eDiary) devices.
- Statistical software is used to analyze the collected data and prepare it for regulatory submission.
- Access to many of these applications are increasingly aggregated in web-based clinical trial portals.

DISSEMINATION ACTIVITIES

- Dissemination plan of the results will try to include publications as well as presenting results at international scientific meetings

Final thoughts

1) Avoid me too research
2) Try to be innovative and SMART (see goals)
3) Apply for funding for your research, even small amounts
4) EU, Bill and Melinda Gates, AMFAR, NIH calls prefer partners from Africa, South America, Eastern Europe etc
5) Form networks and collaborations, link with other centres
6) Apply to be sites in larger multicentre studies - Go to conferences and congresses