DSMB preparation workshop

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Introduction

- Introduction, legal and technical basis
- What is involved on personal level
- Safety, trial design
- Trial analyses
- Examples
- Questions throughout (please)

Introduction, legal and technical

- Data and Satety Monitoring Board
- Small group of independent experts
- Not required for all trials
- Responsible for safety of patients and integrity of research

Requirements for a DSMB

- Generally required for all Phase 3 – but not always. Not required always for earlier Phase or PK and interaction studies for example.
- Generally only companies following good practice
- Where this extends to community DSMB members these are also progressive companies, also generally with HIV, but also some cancer studies. Otherwise this is very rare – but that doesn't reduce the importance.
- Probably best to select strategy for prioritising this representation – independent vs company research? (not included in SMART, EuroSIDA, Esprit etc)
- Advisory role on other issues

Training requirements

- This can be a long list – but is covered by ‘ensuring safety of participants in the trial’
- Role of DSMB is approached as a clearly defined role, with predefined criteria for major roles or interventions
- In practice there are many areas where patient safety perspective is different to trial perspective.
- Think about all the things you learn from ECAB about trial design and safety

Why include community in DSMB?

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- HIV+ people involved in all aspects of our care (Denver 1983)
- This includes steering committees, investigator meetings and advisory boards
- For input into the design of trials –established by ECAB
- For access to ongoing enrollment details, early results and trial difficulties through steering committees and investigator meetings
- Because it is a position that can change and influence patient care
- Relatively rare to include on DSMB – main reason is that DSMB can ask for anything.
- ECAB programme to prioritise future involvement and priorities?
- Share responsibility of risk, responsibility and negative aspects of clinical research

Denver Principles, 1983

Recommendations for PWAs

1. Choose our own representatives, to deal with the media, to choose their own agenda and to plan their own strategies.
2. Be involved at every level of decision-making and specifically serve on the boards of directors of provider organizations.
3. Be included in all AIDS forums with equal credibility as other participants, to share their own experiences and knowledge.
4. Substitute low-risk sexual behaviors; we feel people with AIDS have an ethical responsibility to inform their potential sexual partners of their health status.

Why individuals should join DSMB?

- Represent HIV+ people and ensure trial safety first-hand
- Will give you important experience in the way that trials work
- Develop different relationships with experts
- Opportunity to use these relationships for better community influence

Trials get it wrong

Examples…..?

Trials get it wrong

- Strategy: ACTG 364 – DLV/ADV interaction
- Strategy: ACTG 5095 – Trizivir and other triple nuke
- Strategy: STI and GIGA-HAART
- Early maintenance therapy: IDV monotherapy
- Failed compounds: DPC compounds, capravirine, etc
- At some point someone is seeing data in every study.

DSMB structure

- Different working structure – small working group of experts
- You are included because of your expertise
- Collaboration and consensus working
- DSMB probably only includes 4-6 people;
- Open meetings will include 1-2 company representatives

General requirements

- Understand and commit to the principles of randomised clinical trials (RCT).
- This will sometimes involves different approaches to way that the EACB and EATG works
  - RCT are the basis for evidence based medicine: randomization, placebo, statistical significance etc
  - some people are very likely do better or worse than others
  - by this definition, people consent to take part in research
  - understand issue of confidentiality

Confidentiality and support

- By definition, confidentiality is absolute relating to any information about the data in the trial
- To indicate in the slightest way that things are going well or poorly is something that you have to never do
- This includes friends, partners, colleagues, etc etc
- This is not a contradiction to your interests in representing the community, it is based in believing in basis of RCT and evidence-based medicine
- Any concern about the function of a DSMB, or concerns about the study should be dealt with within the DSMB

How to sort and select information

- Top line results: what to ask for, format to get results
- CD4, viral load, grade 3-4 safety
- Reports will include information on all lab results in complicated tables - you can ask for easier summaries - other DSMB members will

Examples

- Entry criteria and protocol violations
  - If there are CD4 or viral load entry criteria
  - If there are no CD4 or viral load entry criteria
  - Look at way data is presented
  - Extreme examples without unblinding
  - Statistics: mean, SD, median, IQR and range
  - Number at each analysis, statistical significance

Examples

- **Slow enrollment**
  - Think of first patients in the study
  - A study that enrolls slowly will leave those patients on unknown drugs or unproven strategies for the longest time, potentially without DSMB overview
  - Futility and standard of care (Colate)

Examples

- **Serious side effects**
  - Grade 1-2 vs Grade 3-4,
  - HSR, rash, liver, death
  - Frequency of reporting, additional expertise
  - Study population and drug profile
  - At some point ‘should this study continue’?
  - Ask for advice or discussion, can be in a closed session or with chair

Examples

- **Individual patient care**
  - Continued access to trial medication,
  - Within or outside of trial
  - Partial unblinding
  - Acceptability of risk/benefit for different patient groups
  - Changing standard of care

Ethical issues

- Balance individual safety with importance of study question
- Balance issues of confidentiality
- Responsibility for negative trial results

Empowerment

- You are the person getting symptoms
- You are the person taking the treatment
- You have the most vested interest in getting the best treatment and the best quality of life
- Taking an active role will change the way doctors talk to you
- Healthcare resources are always limited, doctors are busy, hospitals are overworked

Empowerment

- We are the people getting symptoms
- We are the people taking the treatment
- We have the most vested interest in getting the best treatment, the best quality of life and the clearest data
- Taking an active role will change the way researchers talk to, and involve the community
- Healthcare resources are always limited, doctors are busy, hospitals are overworked, research is expensive…

Additional slides

Denver Principles, 1983

PWA Self-Empowerment Principles, 1983

(Statement from PWA advisory committee)

- We condemn attempts to label us as "victims," a term which implies defeat, and we are only occasional "patients," a term which implies passivity, helplessness, and the dependence upon the care of others.

  We are "People With AIDS" (PWAs) - later PLWHA.

Denver Principles, 1983

Recommendations for all people

1. Support us in our struggle against those who would fire us from our jobs, evict us from our homes, refuse to touch us or separate us from our loved ones - AIDS cannot be spread by casual, social contact.
2. Not scapegoat PWAs, or blame us for the epidemic or generalize about our lifestyles. Control with media.

Denver Principles, 1983

Recommendations for PWAs

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Denver Principles, 1983

Rights of People with AIDS

1. To have as full and satisfying sexual and emotional lives as anyone else.
2. To quality medical treatment and quality social service provisions without discrimination of any form including sexual orientation, gender, diagnosis, economic status or race.
3. To full explanations of all medical procedures and risks, to choose or refuse their treatment modalities, to refuse to participate in research without jeopardizing their treatment and to make informed decisions about their lives.
4. To privacy, to confidentiality of medical records, to human respect and to choose who their significant others are.
5. To die and to LIVE ... in dignity.

Medical timeline

• Observation or research idea	Y0
• Pilot study	
- design, ethics approval, screen enroll	1-2 years
- run study, preliminary analysis	+6 months
• Conference abstract	+6 months
• Write up paper, submit to publication	+6 months
• Published data	+6 months
• Guidelines and clinical practice	???
Total	3-4 years

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