Design issues in RAC protocols

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- Dr. Dave DeMets
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Research questions

- How frequently do RAC members raise design concerns in written review or public discussion?
- What are the most common concerns?
- How often are design concerns mentioned in the RAC letter to investigators?

How frequently do YOU think these issues were raised?

≤25% 50% ≥75%

- Biostatistical Analysis of AEs
- Dose-escalation
- Selection of Subjects
- Selection of Safety endpoints

How frequently do YOU think these issues were raised?

≤25% 50% ≥75%

- Biostatistical Analysis of AEs 12%
- Dose-escalation 76%
- Selection of Subjects 86%
- Selection of Safety endpoints 76%

Methods

- **Examined protocols publicly reviewed by the RAC from December 2000 through December 2003**
- **44 protocols in total**
  - 2 pairs underwent joint review
  - 42 data points

Methods

Characteristics of the 44 protocols

- 31 (70%) Phase I
- 12 (27%) Phase I/II
- 1 (2%) Phase II
- 37 (82%) employed dose-escalation

Methods

RAC Process	Reviewed for this study
Protocol Selected for Public Review	Protocol
↓	↓
Written RAC Review	Written Comments
↓	↓
Public Discussion	Meeting Transcripts
↓	↓
Final RAC Recommendations	Letter to Investigator

Methods

- **Identified key design issues**
- **Prospectively designed data capture form**
  - Tested and refined on a subset of protocols
- **Grouped issues into major categories each with more specific sub-categories**
  - e.g., Dose-escalation (starting dose, escalation algorithm…)

Methods

- **Identified when issues were raised by one or more committee members**
  - written reviews and meeting transcripts
- **Identified when issues remained unresolved**
  - recommendations in final RAC letter
- **Assignment to categories by agreement**

Results
(n=42)

Design Issues Raised in Review (1)

Selection of subjects	37 (86%)
Dose-escalation	32 (76%)
Selection of safety endpoints	32 (76%)
Biologic outcomes	27 (64%)
Overall study design	23 (55%)

Design issues Raised in Review (2)

Data safety monitoring board	14 (33%)
Selection of efficacy outcomes	12 (29%)
Biostatistical analysis of AEs	5 (12%)
Biostatistical analysis of efficacy outcomes	3 (7%)
Selection of dose for Phase II study	1 (2%)

Frequently Raised Design Issues

Selection of subjects	37 (86%)
Dose-escalation	32 (76%)
Selection of safety endpoints	32 (76%)
Biologic outcomes	27 (64%)
Overall study design	23 (55%)

Selection of Subjects

Request clarification	11 (26%)
Request more precise inclusion/exclusion criteria	14 (33%)
Inclusion of subjects at increased risk	22 (52%)
Disease severity of subjects	14 (33%)
Use of other therapies	8 (19%)

Subject Selection: exclude subjects at increased risk

"The presence of inflammatory track changes in… other human studies where transgenes are injected into the CNS is concerning. Ventriculitis likely is a risk for subjects... Please consider excluding all patients whose gliomas… are in close proximity to the ventricles…"

Frequently Raised Design Issues

Selection of subjects	37 (86%)
Dose-escalation	32 (76%)
Selection of safety endpoints	32 (76%)
Biologic outcomes	27 (64%)
Overall study design	23 (55%)

Dose-Escalation Issues

Request clarification	7 (17%)
Request more information regarding DE scheme	7 (17%)
Time intervals between patients or cohorts	9 (21%)
Escalation Algorithm	8 (19%)

Dose-Escalation: "more cautious approach"

- "For the 3rd and 4th cohorts, one patient [should] be enrolled at a time"
- "Stop the trial if there is one participant death due to excessive bleeding rather than applying the standard three death rule"

Frequently Raised Design Issues

Selection of subjects	37 (86%)
Dose-escalation	32 (76%)
Selection of safety endpoints	32 (76%)
Biologic outcomes	27 (64%)
Overall study design	23 (55%)

Selection of Safety Endpoints

Recommend additional test, assay, or endpoint	20 (48%)
Concern about potential AE	16 (38%)
Recommend modification of protocol to reduce risk	11 (26%)

Safety Endpoints: adequate and appropriate endpoints and assays

"Gene expression in tissues that come in contact with the transgene … [poses a] potential risk [to] distance sight over time."

Recommendation: "conjunctival scrapings of the participants' lower eyelids should be tested for the presence of vector"

Frequently Raised Design Issues

Selection of subjects	37 (86%)
Dose-escalation	32 (76%)
Selection of safety endpoints	32 (76%)
Biologic outcomes	27 (64%)
Overall study design	23 (55%)

Biologic Endpoints

Request further discussion or consideration	10 (24%)
Recommend additional test or assay	20 (48%)
Recommend modification of protocol	10 (24%)

Biologic Endpoints: additional assays

"Plasma, as well as white blood cells, should be analyzed for the presence of vector sequences ... Any tumors that develop in the research participants should be tested for the presence of vector sequences."

Frequently Raised Design Issues

Selection of subjects	37 (86%)
Dose-escalation	32 (76%)
Selection of safety endpoints	32 (76%)
Biologic outcomes	27 (64%)
Overall study design	23 (55%)

Overall Study Design

Sample size rationale	13 (31%)
Use of placebo	10 (23%)
Phase designation	7 (17%)

Overall Design: sample size rationale

"Why 12 patients?... Sample size is determined by statistical consideration affordability, feasibility and so forth…it seems we can put some precision on what we will learn from the number of patients in this study... [we should] begin to quantify what it is we are going to learn."

Unresolved Issues: Recommendations in Letter to PI

Selection of subjects	21 (50%)
Selection of safety endpoints	18 (43%)
Biologic Outcomes	16 (38%)
Dose-escalation	11 (26%)

Subject Safety

- **Composite variable of 15 subcategories encompassing all comments designed to reduce risk to participants, e.g.**
  - time intervals between cohorts
  - additional safety assays or endpoints
  - protocol modification to reduce risk
  - need for DSMB
  - exclude subjects at risk

Subject Safety

- Comments belonging to any one of the specified subcategories was sufficient for inclusion

Subject Safety

Safety-related Design Issues:

- **Raised in RAC review** **39/42 (93%)**
- **Appeared in RAC letter** **28/42 (67%)**

Limitations

- Small N, cannot detect associations
- Do not know what changes were made in protocols after RAC review
- Do not know recommendations of FDA, local IRB
- No comparison to other fields

Conclusions / Next Steps

- Concerns about study design are commonly raised and focus particularly on safety
- Basis for a future guidance document or points to consider

Conclusions / Next Steps

- Many concerns reflect issues common to the field
- Subject for future discussion and collaboration involving the RAC, researchers, and other stakeholders

Back-Up / Supplementary Slides

DSMB Issues

Point of clarification	4 (9%)
Request description of plan for DSMB	5 (12%)
Recommend addition of DSMB	6 (14%)
Recommend modification of plan for DSMB	4 (9%)

DSMB: Additional Oversight Needed

"This phase I protocol should have a DSMB because of its risk. The composition and responsibilities of members need to be detailed… I would feel better if the [DSMB also met for] other things…[such as] changes in the plasma HIV RNA and the CD4 count."

Investigator Experience

- Evaluated by prior submission to RAC
- Did not correlate greatly with # or type of design issues raised by committee
- Only one subcategory “concern regarding antibodies to vector” showed a statistically significant difference (5% for experienced PI’s vs. 19% for first time submitters, p=.04)

Subject Selection: target appropriate disease subset

"Because… in a Phase I study you may be giving up… standard [or effective] therapy… you may want to shift your population [to patients] unlikely to benefit from the standard therapies [and those who] refuse them..."

Overall Design: placebo in Phase 1 study

"[The placebo has] unknown or uncertain toxicity... If the goal of the phase 1 portion is dose finding based on toxicity, the exposure of subjects to risk without benefit is questionable. Certainly, the ability to determine efficacy based on the numbers studied in this phase is minimal."