Pivotal Studies for Demonstrating Efficacy in Haemophilia Therapies

Towards the Next Generation

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Disclosures for: Type name

In compliance with the EACCME* policy, WFH requires the following disclosures be made at each presentation

<table>
<thead>
<tr>
<th>CONFLICT</th>
<th>DISCLOSURE — IF CONFLICT OF INTEREST EXISTS</th>
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<tr>
<td>RESEARCH SUPPORT</td>
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<td>DIRECTOR, OFFICER, EMPLOYEE</td>
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<td>SHAREHOLDER</td>
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<td>HONORARIA</td>
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<td>ADVISORY COMMITTEE</td>
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<td>CONSULTANT</td>
<td>Compensated contractual services to the biotherapeutics industry</td>
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* European Accreditation Council for Continuing Medical Education
The “Gold Standard”

Clinical Trial

- Equipoise
- Randomization
- Blinding
- Controls
“Pivotal” Studies

• Trial designed & executed to get statistically significant evidence of efficacy and safety as required by HAs for NDA / sNDA approval.
• Agent vs placebo/comparator
• Also includes studies with the aim to include claims into the label as well as Post-marketing commitments.
The statistical burden

- A study **must** have an adequate size
- Required Size, based on:
  - Significance level (usually 5%)
  - Minimal clinically worthwhile difference
  - Power (usually 80-90%)
- Results: Test of significance
  - $P<0.05$ = Positive Study
  - $P>0.05$ = Negative Study

<table>
<thead>
<tr>
<th>Relative reduction in event rate (%)</th>
<th>Needed number of events</th>
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<tr>
<td>50</td>
<td>71</td>
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<tr>
<td>40</td>
<td>125</td>
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<tr>
<td>30</td>
<td>252</td>
</tr>
<tr>
<td>20</td>
<td>635</td>
</tr>
<tr>
<td>10</td>
<td>2830</td>
</tr>
<tr>
<td>$\alpha = 0.05$</td>
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<td>power = 80%</td>
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No statistical basis for these patient numbers – just a feeling for “what is possible”
“There is insufficient evidence from randomised controlled trials to determine whether prophylactic clotting factor concentrates decrease bleeding and bleeding-related complications in hemophilia A or B, compared to placebo, on-demand treatment, or prophylaxis based on pharmacokinetic data from individuals. Well-designed RCTs are needed to assess the effectiveness of prophylactic clotting factor concentrates. Two clinical trials are ongoing.”
Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia

Manco-Johnson MJ et al.

“Prophylaxis with recombinant factor VIII can prevent joint damage and decrease the frequency of joint and other hemorrhages in young boys with severe hemophilia A.”
Phase 3 study of rFVIII-Fc fusion protein in severe Haem A

“All 14 of the subjects in the on-demand cohort of the FAS had bleeds. The mean ABR was 33.87 (± 17.37)……These results show that ABRs were lower in subjects who received prophylactic treatment than in subjects who received on-demand treatment ……”

FDA Report
Equipoise

• Requirement for genuine uncertainty within the expert medical community about the preferred treatment.
• “An honest, professional disagreement” among experts about the relative merits of competing interventions (Freedman)
• Uncertainty not necessarily on the part of the individual investigator
• Allows clinical investigators to continue a trial until enough statistical evidence of benefit accrues
Risk and the Concept of Clinical Equipoise

- Clinical equipoise is the preferred moral basis for the RCT
- Premise: it is unethical to give subjects interventions known to be inferior
- Placebos are acceptable only when
  - No standard treatment exists
  - Standard treatment involves intolerable risks

Are we at equipoise in regard to prophylaxis versus on demand therapy?
The EBM Pyramid
According to the Cochrane Collaboration

“The paradox of the clinical trial is that it is the best way to assess whether an intervention works, but arguably the worst way to assess who will benefit from it.”

“The benefit or harm of most treatments in clinical trials can be misleading and fail to reveal the potentially complex mixture of substantial benefits for some, little benefit for many, and harm for few.”
R Kravitz, Milbank Quarterly, 2004
RCTs have focused on identifying interventions that are effective, on average, across a broad patient population. However,

- Interventions that yield a statistically significant treatment effect across a study population may be ineffective for some patients and harmful for others.
- Interventions that do not yield a statistically significant treatment effect across a study population may work for certain subsets of the population.
What is Personalized Medicine?

Personalized medicine (PM) is the tailoring of medical care to the particular traits (or circumstances or other characteristics) of a patient that influence response to a health care intervention. It is based on the ability to classify patients into subpopulations that differ in their responses to particular interventions.
Personalizing Prophylaxis

Effect of variability of FVIII $t_{1/2}$

![Graph showing the effect of variability of FVIII $t_{1/2}$](#)
The log-normal distribution of individually estimated clearance (mL/h per kg) in the 100 adolescent/adult patients.
Personalizing Prophylaxis

Variation in post-infusion FVIII

Observed FVIII levels (n = 2035) plotted against time after the infusion.

PK guided personalized prophylaxis

Eligible patients
- 7 to 65 years of age
- FVIII ≤2 IU/dL
- Previous episodic treatment for ≥12 months and ≥15 EDs
- ≥8 lifetime joint bleeds before study entry

72 hour washout

PK evaluation

Episodic therapy for 6 months

Randomization

Standard prophylaxis (20–40 IU/kg q 48±6 hours)

PK-guided prophylaxis (20–80 IU/kg q 72±6 hours)

12 months

Assessments
- ABR
- FVIII trough levels
- Treatment of bleeding events
- PK
- HRQOL

End of study

OD

All Prophy

Biologics: Targets and Therapy 2014:8 115–127
Hierarchy of strength of evidence of therapeutic efficacy

1. “N of 1” randomized controlled trial
2. Systematic reviews of randomized controlled trials
3. Single randomized controlled trial
4. Systematic reviews of observational studies
5. Single observational study
6. Physiological studies
7. Unsystematic clinical observations

N of 1 trials
Trial of therapy

- Randomized clinical trial used in just one patient
- Patient undergoes pairs of treatment periods
  - one period is the experimental treatment
  - other period is the comparator (placebo or alternative treatment)
- N of 1 trials are considered to provide the strongest level of evidence about the existence of a causal relationship between a treatment and an outcome.
- Do not permit any generalization of the findings on the individual patient to any patient population.
N of 1 trails
Trial of therapy

• BUT - may be combined
  • through meta-analysis
  • through a Bayesian random effects model

• Combination provides a population estimate for treatment effectiveness while retaining the capacity to provide a distinct effectiveness estimate for each individual patient
Typical N-of-1 trial.

The order of treatment and placebo are randomly assigned for each cycle.
Therapies suitable for N-of-1 trial

• Condition for which the medication is being prescribed is chronic and [relatively] stable
• Half-life of the medication being tested is short
• Rapid onset/offset of biological action of the medication
• Effect of the medication can be measured using a validated outcome measure
• Medication does not alter the underlying condition
  • (ie does not cure – NA for GT)
Regulatory measures.....

Guidance for Industry

Adaptive Design Clinical Trials for Drugs and Biologics

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2010
Clinical/Medical
Declaration of Helsinki
(Abandoned by the FDA in 2008)

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic method.

➢ Does randomizing patients to OD and prophylaxis arms conform to this?

See “Is the Developing World the Answer? - Unethical clinical trials in the Third World” - Sammy Almashat, MD, MPH, Sidney Wolfe, MD, Public Citizen’s Health Research Group
A placebo-controlled trial may be ethically acceptable:

- Where for **compelling scientifically sound methodological reasons** its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a **minor condition** and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

What is the **compelling scientifically sound methodological reason** for exposing patients to the high ABR’s of OD therapy?

Is haemophilia a **minor condition**?
Declaration of Helsinki

- Paragraph 30: At the conclusion of the study, every patient entered into the study should be assured of **access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study**.

- "Clarification": It is necessary during the study planning process to identify **post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care**. Post-trial access arrangements or other care **must be described in the study protocol** so the ethical review committee may consider such arrangements during its review.

Is this being done for the patients on trials for CFCs?
This study revealed a substantial amount of cost-savings for insurance companies generated by free drugs given via sponsored clinical trials. Sponsored clinical trials may minimize the total drug expenditures of a hospital, which is beneficial under a reimbursement policy that mandates control of drug expenses.

The participation in sponsored clinical trials in which drugs are provided free of charge offers substantial cost savings for the National Health Service; moreover, the grants received for each enrolled patient produced additional income.
Summary

• Pivotal studies for haemophilia therapies need to transcend the current EBM paradigm.
• In particular, small patient numbers and knowledge of PK suggest a personalized approach.
• The N of 1 trial approach seems worthy of exploration as a route to efficacy assessment.
• Randomization of patients into on demand therapy is no longer acceptable.
• Clarity is needed to establish that patients on studies continue to benefit from optimal treatment.
• The large number of patients on trials may lead to complacency from funding agencies.

All solutions are possible if

THE PATIENT COMES FIRST
“I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone.”

Hippocratic Oath

“and there shall be no more death, neither sorrow, nor crying, neither shall there be any more pain: for the former things are passed away”

Revelations Ch21