Payment Policies' Impact on Clinical Trials Participation

Neil M. Bressler, MD
Chief, Retina Division – Wilmer Eye Institute
Johns Hopkins University School of Medicine

Financial Disclosures

- Grants to investigators at The Johns Hopkins University are negotiated and administered by the institution which receives the grants, typically through the Office of Research Administration. Individual investigators who participate in the sponsored project(s) are not directly compensated by the sponsor, but may receive salary or other support from the institution to support their effort on the project(s).
- Sep 2007: Neil Bressler is Principal Investigator for the following: Acucela, Allergan, AstraZeneca, Athenagen, Carl Zeiss Meditec, EMMES, Apeliotus Technologies, Fovea, Genentech, JAEB, JDRF, Jerini, Merck, Notal Vision, Inc., Novartis, Ortho Clinical Diagnostics - J&J, Othera, Oxigene, Pfizer, QLT, Regeneron, Schering Plough, TargeGen.
- Neil Bressler's wife receives consulting payments from Genentech for DSMC work and Notal Vision.

Experience with Payment Policies in Clinical Trials

- Chair: National Eye Institute sponsored Submacular Surgery Trials
  - Group H Trial: Median age 48 years
  - Group N Trial: Median age 77 years (54-92)
  - Group B Trial: Median age79 years (57-94)
- Costs assumed that subjects and their third party payors would cover costs of standard care which occurs simultaneous to study visits or procedures

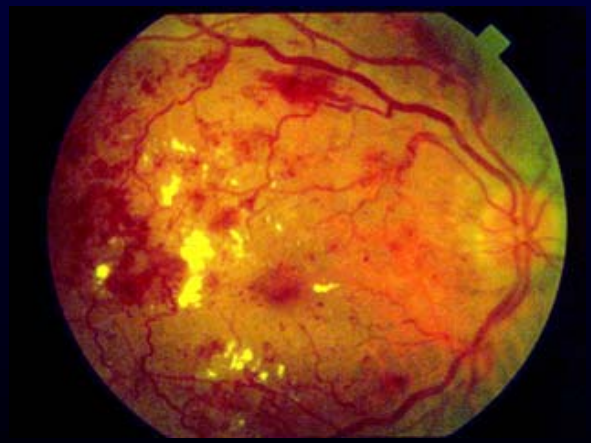
Subjects with Financial Hardship (e.g., no insurance)

- Subjects without insurance for standard care which also is part of research:
  - Individual investigator to manage as is done with financial hardship of patient, which in most cases is to waive most or all of the costs.
  - These waivers constitute a cost sharing by the clinical center with the National Eye Institute
- Challenges
  - Change of insurance during trial
  - Costs out of investigator's control (e.g., anesthesia during surgery, facilities)
  - PI for Chair's Office and Coordinating Center manage on a case-by-case basis following written guidelines and policies

DRCR.net

Impact of Payment Policies on Diabetic Retinopathy Clinical Research Network (DRCR.net)

Dedicated to multicenter clinical research of diabetic retinopathy, macular edema and associated disorders.



National Eye Institute
NATIONAL INSTITUTES OF HEALTH

DRCR Network Overview

- **Funding:**
  - **National Eye Institute-sponsored cooperative agreement initiated September 2002.**
- **Objective:**
  - **The development of a collaborative network to facilitate multicenter clinical research on diabetic retinopathy, diabetic macular edema and associated conditions.**

Priority Initiatives

- **Involvement of community-based practices, as well as academic centers.**

- ***Collaborate with industry*** **to facilitate investigations and pursue opportunities otherwise not possible and to do so in a manner consistent with the Network's dedication to academic integrity and optimal clinical trial performance.**

Current DRCR Network Status

- **Overall Network Participation** (as of 1-24-07)
  - 146 active or pending sites, 180 sites submitted application for network
    - 93 community based sites
  - 429 total Investigators;
  - 895 additional personnel
  - 40 States

DRCR Network Protocols (as of June 30, 2007)	# of Subjects
Pilot Study of Laser Photocoagulation for DME (A)	263
Randomized Trial: Intravitreal Steroids vs Focal Laser for DME (B)	693
Temporal Variation in OCT Measurements in DME (C)	107
Evaluation of Vitrectomy for DME (D)	186
A Pilot Study of Peribulbar Triamcinolone Acetonide for DME (E)	113
Observational Study: Development of DME After PRP (F)	155
Subclinical Diabetic Macular Edema Study (G)	82
Phase 2 Randomized Trial of Bevacizumab for DME (H)	121
Laser-Ranibizumab-Triamcinolone for DME (I)	132
Laser-Ranibizumab-Triamcinolone for PDR (J)	24
Laser Response Protocol (K)	128
DRCR Network Study Subject Total	**2,004**

DRCR Network Protocols (as of June 30, 2007)	# of Subjects
Pilot Study of Laser Photocoagulation for DME (A)	263
Randomized Trial: Intravitreal Steroids vs Focal Laser for DME (B)	693
Temporal Variation in OCT Measurements in DME (C)	107
Evaluation of Vitrectomy for DME (D)	186
A Pilot Study of Peribulbar Triamcinolone Acetonide for DME (E)	113
Observational Study: Development of DME After PRP (F)	155
Subclinical Diabetic Macular Edema Study (G)	82
Phase 2 Randomized Trial of Bevacizumab for DME (H)	121
Laser-Ranibizumab-Triamcinolone for DME (I)	132
Laser-Ranibizumab-Triamcinolone for PDR (J)	24
Laser Response Protocol (K)	128
DRCR Network Study Subject Total	2,004

Impact of Payment Policies in DRCR.net

- Protocol B (Intravitreal Triamcinolone Trial): 43% >=65 years
- Protocol I (Ranibizumab-Triamcinolone-Laser Trial): 45% >=65 years
- Sham vs true intravitreal injections
  - Cannot charge subject for standard care injection without unmasking

Injections in Network studies are double-masked (subject and outcome assesor)

Sham Versus No-Treatment Controls

Is there evidence of an experimental "placebo effect"?

- **Cochrane systematic reviews (2003, 2006) by Hröbjartsson and Gøtzsche.**
- **156 trials in many medical conditions with controls randomly assigned to placebo or sham versus no treatment.**

Conclusion: *Hröbjartsson and Gøtzsche:*

- **“unable to detect a statistically significant overall effect of placebo intervention in trials with binary outcomes whether reported by patients or by observers, or in trials with continuous outcomes reported by observers.”**
- **“moderate difference . . . for trials with continuous outcomes reported by patients, and for trials involving patient-reported pain and phobia.”**
- **“No evidence that placebo interventions in general have clinically important effects.”**

Payment Policies in DRCR.net

- List of each procedure at each visit:
  - Visual acuity measurement – study budget
  - Retina imaging – standard care/study budget
  - Eye exam – standard care/study budget
  - Coordinator time – study budget
  - Investigator time – study budget
  - Laser treatment – standard care
  - Injection – study budget

Different Combinations of Therapy

- **Some subjects get laser and no injections, combination of monthly injections and laser, combination of injections up to 3 times a year and laser**

Payment Policies in DRCR.net

- Total per subject in Year 1:
  - Study budget sham: $4,395
  - Standard care sham: $2,960
  - Study budget monthly drug + laser: $6,995
  - Standard care monthly drug + laser: $2,960
  - Study budget monthly drug alone: $6,995
  - Standard care monthly drug alone: $1,460
  - Study budget tri-annual drug + laser: $5,175
  - Standard care tri-annual drug + laser: $2,960
- 700 subjects
- Study continues in Year 2 and Year 3

Conclusions: Impact of Payment Policies in Ophthalmology Trials

- Third party payments have been critical to operation of clinical trials in ophthalmology
- Many subjects are relevant to CMS
- Cost sharing with investigators' practice occurs
- Clear payment schedules (study budget vs standard care) are needed at onset of study
- Central case management with consistent guidelines and policies are needed
- Masking should be used prudently - raises study costs considerably