審查類型與完整審查

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Identifying Intent

- Research：A systematic investigation, including research development testing, and evaluation, designed to develop or contribute to generalizable knowledge.
- The major goal of research :

  benefit other than research subject
- NOT research (no IRB review) : Quality improvement / QA activities, Case report, Innovative therapy, Outcome analysis, Resource utilization review, Education

Criteria for approval of research

- 21 CFR 56, Sec.111
- Criteria
  - 對受試者的 risks 應該是最小的
  - 參與試驗對受試者可能產生的 risks / benefits 應該合理
  - 受試者的選擇應該是 equitable
  - 應由subject or subject's legally authorized representative取得 Informed consent
  - Informed consent 應被 documented
  - 應適當的監測以確保受試者的安全
  - 保護 the privacy of subjects 並維持 the confidentiality of data

Review Categories

- Exempt Review
- Expedited Review
- Full-Committee Review

Exempt Review 2-1

- **45 CFR 46 : 101(b) – minimal standards**
  - 常規的 educational practices and setting
  - 匿名的 educational tests, surveys, interviews, or observations
  - 可辨識的 subjects in special circumstances
  - 收集或研究既有的 data
  - Public benefic or service programs
  - 評估 taste and food 與接受度的研究

Exempt Review 2-2

- FDA does not exempt any research, except :
  - Emergency circumstance
  - Taste and food quality studies
- Vulnerable groups
  - No exempt – prisoners, children
  - No exempt – 觀察 minors public behavior (除非 PI 不在其中)
  - Exempt – pregnant women, human fetus, and neonates （ 45 CFR 46, Subpart B ）

Expedited Review 2-1

- **DHHS & FDA**
  - No more than minimal risk
  - Minor changes in previously approved research
- **Minimal risk**
  - Not great than daily life
    (or routine exam. or test)
  - No change at “risk-benefit relationship”

Expedited Review 2-2

- **Can be conducted by :**
  - IRB Chair
  - IRB members designated by the Chair
    - Experienced reviewers
    - Voting members
  - A subcommittee of the IRB
- **Reviewers**
  - Can “approve” or “require modifications”
  - No “disapproval” – refer to full board review

Criteria for Expedited Review

- 有完整的 research design, 最好是已經在病人身上使用過的 procedures
- 受試者可能的 risks / benefits 應該合理
- 受試者的選擇應該是 equitable
- 應取得 Informed consent 並有紀錄可查
- 應有可以收集並監測 data 的計畫來確保受試者的安全
- 保護 the privacy of subjects 並維持the confidentiality of data
- 對 vulnerable subjects 應有額外的保護措施

Compassionate use

- DHHS & FDA : no compassionate use
- FDA accept “Emergency use” ：
  - Life-threatening, 且目前沒有可用的治療方式
  - 沒有足夠的時間進行 full board review
  - 僅用於一位病人身上
  - 應於 5 days 內通知 IRB
- DHHS
  - Not provide for an emergency exception
  - Allow “emergency medical treatment”

Waiver of Consent in Emergency

- 在 emergency medicine research 可免除同意書
- 僅限於下列二項：
  - 在FDA regulation下的,尚未核准上市的 investigational intervention
  - 由 federal agency 所贊助,或是由一個所有其他研究都依從federal regulations的機構執行
- 有 8 種情況可允許免除同意書

Waiver of Consent 3-1

1. 受試者已處於 life-threatening 的情況，但目前可考慮的處理方式不是 unproven 就是 unsatisfactory
2. 不可能得到 informed consent
   - a life-threatening situation
   - 無法在給與 intervention 前得到 consent
   - 無合理的方法來確認受試者是否有能力參與
3. 預期可對受試者帶來 direct benefit
4. 不免除同意書就無法進行

Waiver of Consent 3-2

5. 研究有足夠的科學證據證明其有效, PI 承諾會盡快和 LAR 連絡
6. IRB 仍應審查並同意其 IC, 並應在可能情況下盡快取得受試者的簽署
7. 應提供 Additional protection
   - 先和社區的代表協商
   - 應在執行前先於社區公開
   - 執行完成後應於社區公開並致謝
   - 應建立獨立的 data monitoring committee
   - 若找不到法定代理人,PI 應聯絡其家屬並有紀錄
8. 受試者情況改善應盡快告知, 若死亡也應告知關係人

Waiver of Consent 3-3

- 向 FDA 申請時必須清楚說明將無能力 consent 的受試者納入的原因
- IRB 必須以書面記載有一位有執照的醫師確定waiver是可被允許的
- 這位有執照的醫師必須是的 IRB 委員或 consultant, 而且必須沒有參與此試驗
- 免受試者同意書不適用下列族群: fetuses, pregnant women, human in vitro fertilization, and prisoners

Reviewer Worksheet 2-1

- Introduction, Specific Aims, Background, and Significance
- Scientific Design
- Research Procedures
- Inclusion/Exclusion Criteria
- Statistic Analysis and Data Monitoring

Reviewer Worksheet 2-2

- Privacy and Confidentiality
- Recruitment
- Compensation and costs
- Potential Risks/Discomforts and Benefits
- Informed Consent/Assent
- Other Issues and Consideration

Advantages of using a Reviewer Worksheet

- 有助於促進委員進行完整且具一致性的審查
- 書面記載 IRB 有確實執行審查作業
- 有助於 IRB 遵從 DHHS 和 FDA 的 regulations
- 教育 IRB 委員正確的 review process

Evaluating Study Design and Quality 2-1

- Ethical Codes
  - Nuremberg Code, 1949
    - Point 3 : The experiment should be so designed and base on the results of animal experimentation…
  - Declaration of Helsinki, 2000
    - Sec. 11 : …must conform to generally accepted scientific principles..
    - Sec. 18 : only be conducted if the importance …outweighs the inherent risks and burdens to subject
    - Sec. 29 : the …of a new method should be test against those of the best current prophylactic, diagnostic, and therapeutic methods

Evaluating Study Design and Quality 2-2

- Federal Regulations
  - DHHS & FDA
  - 45 CFR 46, 111(a)
    - Risks to subjects are minimized
    - Risks to subjects are reasonable to benefits
    - The importance of the knowledge may reasonably be expected to result

The Study Population 2-1

- Selection of subjects is equitable :
  - 45 CFR 46, 111 (a) (3)
  - 21 CFR 56, 111 (a) (3)
- IRB 評估的三個 criteria :
  - 研究的目的
  - 執行研究的背景
  - 受試者為vulnerable population 的特殊考慮

The Study Population 2-2

- Equitable subject selection 的原則：
  - 應留意 target population 及 recruitment 的態度和方式
  - 研究選擇的population是否和研究的目的有關
  - 當排除某一族群的人要有很好的科學依據
  - 要有合理的 inclusion/exclusion criteria

Community Consultation

- Common Rule : 46.107 (a)
- 特別針對受試者為弱勢族群的研究
- 諮詢對這一族群深入瞭解或曾和這些族群有豐富相處經驗的專家, 可改善 human research protection, 並減少 group harms
- Group Risks 的形式:
  - 內在或外在的基因的污名化
  - 損壞部族的價值
  - 增加健康照護體系的不信任

Privacy and Confidentiality

- Belmont Report :
  - respect for persons
  - Beneficence
- Privacy and Confidentiality
  - Privacy : people
  - Confidentiality : data (information)
- Harms
  - Psychological distress
  - Loss of Insurance or Employment
  - Damage to Social Standing
- 45 CFR 46.111 (7) & 21 CFR 56.111 (7)
- FDA Information Sheet : Recruiting Study Subjects

Recruitment of Research Subjects 2-1

- Informed Consent : a process
- The beginning : Recruitment
- Information : clear, accurate, and sufficient
- 招募受試者的主要方式：
  - Investigator 自己的病人
  - 由別的醫師轉介來的病人
  - 藉由廣告招募的受試者

Recruitment of Research Subjects 2-2

- **Unethical problems :**
  - Information
    - 不正確的 information
    - 錯誤的 information
  - Comprehension
    - 表達的方式
    - 溝通的方式
  - Voluntariness
    - 脅迫
    - 過度影響

Advertisement for Research

- **The advertisement**
  - Flyers
  - Posters
  - Brochures
  - Media
  - Recruitment letters
- **Advertisement 應有的內容：**
  - PI and /or research facility 的名字和地址
  - 研究的狀況and /or 研究的目的
  - 以 summary 的方式描述納入的條件
  - 以摘要列出參加試驗可能有的 benefits
  - 參與試驗需額外付出的時間和義務
  - 研究地點和獲取進一步資料的聯絡人或辦公室

List of Recommendations

- 清楚說明此計畫為 research
- 避免低估 risks 並高估 benefits
- 不能宣稱 safety, equivalence, or superiority
- 避免不適當的字句,如 “new treatment”, “new medicine”, or “new drug”
- 避免對於相關的治療 procedures 使用 “free”的字眼
- 不能強調 “compensation”
- 在張貼廣告之前應獲得相關單位的同意

Paying Research Subjects 2-1

- **Payment**
  - Expenses
  - Compensation for injury
  - Recognition for time and effort
- **Regulations**
  - DHHS : minimize the possible of coercion or undue influence
  - FDA : neither endorses nor prohibits
  - ICH : no firm guidance
  - CIOMS : ethical and obligation

Paying Research Subjects 2-2

- **Prorating payment**
  - FDA 清楚的要求應依照試驗的 duration 來給與 payment
  - 不可在完成全部的試驗後才給與 payment
  - 應在 IC 內清楚的描述 payment 的方式
- **IRB Responsibilities**
  - 應發展出判斷 payment 適當性的規範
  - 應強調 prorating compensation 的必要性
  - 應提出和 minors 相關的敏感性議題的規範

Provisions for Data Monitoring

- **Data monitoring 的三個基本選擇：**
  - **An Individual Investigator : PI**
  - **A Group Representing the Sponsor**
  - **A DSMB :**
- **Situations for a DSMB :**
  - 研究設計具有一些危險的因素 (如 **Phase III**)
  - 研究的 **risk level** 高 **&** 有較多參與研究的單位
  - 其他因素：**blinding, vulnerability of study population**

Conflict of Interest : Researchers 2-1

- The “motives” may be questioned
- 造成研究者 COI 的因素：
  - 增加研究經費
  - 增加在同一領域的競爭性
  - 商業利益的介入
  - 研究成功能獲得很高的報酬
  - 對 PIs 和 institutions 有因參與試驗而直接得到的報酬

Conflict of Interest : Researchers 2-2

- **Regulations**
  - Declaration of Helsinki, 2000 (disclosure)
  - Public Health Service, 1995 (disclosure)
  - The Final Rule : threshold ($10,000)
- **處理 COI 的方式 : disclosure**
  - To government : FDA, PHS…
  - To the institution : federal funds
  - To the IRB : part of protocol review
  - To subjects : through IC process

Conflict of Interest : Recruitment Incentives

- **Promote enrollment of subjects :**
  - Payments and other inducements to PIs
  - Research staff
  - Referring physicians
- **Potential COI :**
  - 金錢的誘因
  - 金錢之外的特權或獎賞
    - 禮物
    - 研究完成後的獎勵
    - 發表文章
    - 以後參與試驗的機會

Conflict of Interest : IRB

- **Individual Level:**
  - 由 members 主導的研究
  - Members 本人的經濟利益
  - 對同儕的忠誠
  - Member 專長領域的同行競爭
  - 決定可能產生的衝擊
  - 個人的 agendas
  - 委員 Non-IRB 的角色

Conflict of Interest : IRB

- **Institutional Level:**
  - Pressure or desire to protect institution
  - Concern for institution's reputation or prestige
  - Promoting research versus protecting subjects
  - Potential liability
  - Institutional or community values
  - Pressure for speedy reviews
  - Institutional equity or ownership
  - Review fees

Questions ???