Human Subjects Update 2007
Grand Rounds
Research Ethics Series

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- Twenty things You (probably) didn't know about Charles Darwin
- 1. Born on same day as President Lincoln
  - Called Charlie or Bobby as a boy
  - Nicknamed "Gas" as a teen
    - Reference to his penchant for smelly chemical experiments

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 2. Unremarkable student
  - Father considered him lazy
  - "he cared for nothing but shooting dogs and rat-catching"

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Human Subjects Update 2009

- Device development
  - General principles
  - GAO report to Congress (January 2009)
- SAE (Serious Adverse Event) reporting
  - General principles & problems
  - FDA recommendations (January 2009)
- Using one's own children as research subjects
  - New York Times article 01/18/09
  - New York Times video 01/18/09

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Drug Development: IND Investigational New Drug

- 4 Phases
- Pre-clinical
- Phase 0
- Phase 1
- Phase 2
- Phase 3
- Phase 4

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Drug Development: IND Investigational New Drug

- Pre-clinical studies
  - In-vitro
  - In-vivo (animal)
  - Wide dose ranging
  - Looking for efficacy, toxicity and pharmacokinetic information

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Drug Development: IND Investigational New Drug

- Phase 0
- in accordance with FDA 2006 Guidance on Investigational New Drug (IND) Studies
  - designed to speed up the development of promising drugs
- First in human studies
- Microdosing, single dosing
- Pharmacokinetic/pharmacodynamic behavior in humans
  - Not safety or efficacy

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Drug Development: 4 Phases

- Phase 1
  - Small numbers (10-80) healthy volunteers or end stage/no option participants
  - Safety & tolerability
  - Pharmacokinetics & pharmacodynamics

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Drug Development: 4 Phases

- Phase 2
  - Larger numbers (20-300)
  - Efficacy (& safety continues)
  - Where most drugs fail
- 2 A
  - Dose ranging
  - Toxicity
- 2 B
  - Efficacy of chosen dose(s)

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Drug Development: 4 Phases

- Phase 3
  - Larger numbers (300-3,000)
  - Longer duration
  - Multi-center, placebo controlled randomized clinical trials
  - “Gold standard”

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Drug Development: 4 Phases

- Phase 4
- Post Marketing Surveillance Trial
  - Large number safety
  - Long term safety
  - Long term clinical outcomes
  - Head to head comparison
  - Introduce providers to drug

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Device Development

- FDA is responsible for ensuring that medical devices sold in the US provide reasonable assurance of safety and effectiveness and do not pose a threat to public health
- Medical devices include items used for the diagnosis, cure, mitigation, treatment or prevention of a disease
- Devices run the range from simple tools like bandages and surgical clamps to complicated devices like pacemakers and defibrillators

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Device Development: 3 classes

- **The Medical Device Amendments of 1976 established three classes of medical devices**
- **Class I the lowest and class III the highest**
- **The risk the type of device poses to the patient or the user is a major determining factor in the class it is assigned**

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Device Development: 3 classes

- **Title 21 CFR parts 862-892**
- **Device types:**
  - **Class I devices**

    Compliance with general controls (eg GMP) are sufficient to provide reasonable assurance of their safety & effectiveness

    Examples: tongue depressors, elastic bandages, reading glasses, forceps

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Device Development: 3 classes

- **Class II devices**
  - **Subject to general controls and may also be subject to special controls**

    Such as post market surveillance
  - **May support or sustain human life**

    If so, FDA must examine, identify and describe the special controls necessary to provide assurance of their safety & effectiveness
  - Examples: EKG machines, powered bone drills, thermometers

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Device Development: 3 classes

- **Class III devices**
  - **Those for which insufficient information exists to determine whether general & specific controls are sufficient to provide a reasonable assurance of the safety & effectiveness of the devices**

    and
  - **that support or sustain human life or**

    are part of substantial importance in preventing impairment of human health or

    that present a potential for unreasonable risk of illness or injury

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- **3. For a time, at his parents insistence, Darwin aspired to be a doctor,**
  - **but he loathed the sight of blood & quit.**

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- **4. Eventually, he earned a degree in Theology from Cambridge University**

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Device Development: FDA Premarket Review

- Premarket Approval (PMA)
- Premarket notification (510(k))
- Exemption

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Device Development: FDA Premarket Review

- Premarket Approval (PMA)
- Most stringent
- Manufacturer must provide evidence (typically clinical data) giving reasonable assurance of safety & effectiveness
- Successful submission results in FDA approval

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 5. Darwin loved collecting things, esp. beetles. It's said he lost a girlfriend in college because he paid more attention to his bugs than her.
- True story: One day, on a walk through the English countryside for new specimens, finding an interesting beetle, he picked it up & moved on to another which he also picked up. Then he spied a really interesting specimen. Not wanting to relinquish the other two beetles he already had, Darwin popped one of them into his mouth for safe keeping. The insect quickly emitted a noxious spray, prompting Darwin to spit it out and also dropped the other two & went home empty handed.

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 6. The exploratory voyages on the HMS Beagle were to cover two years but lasted almost 5 (1831-1836).
- Darwin was hired more to be companion to ships captain than naturalist.
- Darwin shared a 10 x 11 ' cabin with 2 other men. Part of the cabin was taken up by a mast
- Darwin was chronically seasick.

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Device Development: FDA Premarket Review

- Premarket Notification (510 (k))
- Manufacturer must demonstrate to FDA new device is *substantially equivalent* to device already legally on the market that does not require a PMA
- Successful submission results in FDA clearance

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Device Development: Premarket Notification (510 (k))

- *Substantial equivalence* (*substantially equivalent)* :
  - — device has same intended use as another legally marketed device and the same technological characteristics

    or

    different technological characteristics and submitted info demonstrates device is as safe and effective as legally marketed device and does not raise different questions of safety or effectiveness

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Device Development: FDA Premarket Review

- Premarket Notification (510 (k))
- Established in 1976
- Manufacturer must notify FDA 90 days before it intends to market a device

  and
- must demonstrate to FDA new device is *substantially equivalent* to
  - a device already legally on the market that does not require a PMA

    or
  - a preamendment device (PMA was not required)

    Problem: current device could be 20th or > iteration
- Successful submission results in FDA clearance

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Device Development: FDA Premarket Review 510k v PMA

- 510 (k)
- Less stringent
  - Clinical data not required
  - SE determination based on comparative device descriptions (including performance data)
  - Manufacturing establishments generally not inspected
- Faster
  - FDA 2009 goal 90% in 90 days; 98% in 150 days
  - 60% in 180 and 90% in 295 for PMA's
- Less expensive
  - $18,200 v $870,000 for PMA (averages)

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 7. During the Beetles travels Darwin produced 368 pages of zoology notes, 1,383 pages of geology notes and as 770 page diary. He also collected 1,529 specimens preserved in alcohol and 3,907 dried specimens.

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 8. In 1834, for Darwin' s 25th birthday, the Beagles captain named a mountain ((8,163 ft el.) after him in Tierra del Fuego (group of islands off Argentina coast).
- There are also mountains named after Darwin in Antarctica, Tasmania and CA

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Device Development: FDA Premarket Review

- Exemption
- Many devices are exempt from premarket review
- Most Class 1 and some Class 2 devices are in this exempt category
  - Manufacturer must still register & list devices with FDA
- Humanitarian Device Exemption (HDE)
  - A means of entering the market, for a small # of devices, by other means, without adherence to certain requirements
  - used for devices benefiting patients with rare diseases or conditions.

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Device Development: FDA Premarket Review Exemption

- 67% of the more than 50,000 separate devices listed with FDA between 2003-2007 were exempt from premarket review
- 95% were class I devices
- 5% were class II devices
- (none were class III)

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Device Development: SR v NSR

- The Investigational Device Exemption (IDE) regulations [21 CFR part 812] describe two types of device studies, "significant risk" (SR) and "nonsignificant risk" (NSR).
- An SR device study is a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject
  and
- (1) is intended as an implant
- (2) is used in supporting or sustaining human life
- (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health
- (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- NSR device is defined as not being an SR device

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Device Development: Critical Role of IRB

- The IRB makes this determination
  — With input from sponsor
- NSR devices can be studied without even notifying FDA
- SR devices need FDA approval and go through premarket review under an IDE

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 9. At Cambridge he belonged to the "Gourmet Club" and weekly dined on fare like hawk, bittern (heron family) and owl.
- On HMS Beagle voyages ate puma ("tasted like veal"), iguanas, giant tortoises, armadillos and agoutis (a large rodent that Darwin claimed to be "the best meat I ever tasted").
- In Patagonia Darwin ate Rhea (an ostrich like bird). Ironically he was searching for this species. When he discovered this, he stopped eating and sent the unconsumed portion to the Zoological Society in London, which eventually declared it a new species and named it *Rhea darwinii.*

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 10. In 1839, at the age of 29, Darwin married his first cousin, Emma Wedgewood.
- In writing down the pros & cons of getting married, he determined having a wife was "better than a dog anyhow".
- Charles & Emma remained married for 43 years and had 10 children; seven survived to adulthood.

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Device Development: FDA Premarket Review

- The class I & II devices subject to premarket review are , in general, required to obtain FDA clearance through the 510 (k) process
- Class III devices go through the PMA process
- Certain class III devices in commercial distribution in the US before 5/28/76 (called preamendment devices) and those postamendment devices determined to be substantially equivalent to them may be cleared through the 510(k) process until the FDA publishes regulations either requiring them to go through the PMA process or reclassifies them to a lower class
- Thus Congress envisioned class III devices would, generally, be approved by the more stringent PMA process and premarket review of class I & II devices would entail a lesser degree of scrutiny

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Device Development: FDA Premarket Review

- The Safe Medical Devices Act of 1990 (SDMA) required FDA to:
- Reexamine the preamendment class III device types for which PMA's were not yet required to determine if they should be reclassified to class I or II or remain class III
  and
- Establish a schedule to promulgate regulations requiring those preamendment device types that remain in class III to obtain FDA approval through the PMA process
- Thus all class III devices are eventually to be reviewed through the PMA process

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 11. Darwin loved music but was tone deaf.
  - — Each night of his marriage he would spend a half an hour listening to Emma play the piano (she was trained by Frederic Chopin).
- Darwin & Emma also played two games of backgammon every day
  - — Darwin kept a running score for almost 40 years
  - — Emma usually won

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 12. Emma read novels to Darwin twice a day
  - — He preferred stories with happy endings
  - — He was fond of Jane Austen and Charles Dickens
    - (in 2000, Darwin replaced Dickens on the English 10 pound note)
  - — Darwin found Shakespeare to be "so intolerably dull that it nauseated me".

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GAO Report to Congress on Medical Devices (January 2009)

- Resulted from FDA Amendments Act of 2007
  - — Mandated that GAO study FDA's premarket review of devices under 510(k)
- Discusses the premarket review process (510(k) or PMA) FDA used to review Class I, II & III device submissions between 2003-2007

and

- The extent to which FDA has determined that the devices reviewed through the 510(k) process had new intended uses or new technological characteristics
- Review occurred from 3/08-1/09
- Included review of FDA data base & interviews with FDA officials

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GAO Report to Congress on Medical Devices (January 2009)

- FDA reviewed all the 13,199 submissions for class I & II device through the 510(k) process
  - — 90% cleared for marketing
- FDA reviewed 342 submissions for class III devices through the 510(K) process
  - — 67% cleared
- FDA reviewed 217 original PMA submissions and 784 supplemental PMA submissions
  - — 78 and 87% respectively, approved

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GAO Report to Congress on Medical Devices (January 2009)

- Congress envisioned that class III devices would be approved through the PMA process and the SDMA required that FDA establish a schedule for doing so
- Results: FDA cleared 24 class III device types through the 510(k) process
- These submissions tended to be implantable or life-sustaining or to pose a significant risk to health, safety or welfare of a patient
- As of 10/08, 4 of 24 device types had been reclassified and 20 class III devices could still be cleared through the 510(k) process
- Conclusion: the process remains incomplete

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GAO Report to Congress on Medical Devices (January 2009)

- Note: while FDA officials acknowledged the importance of publishing regulations requiring PMA submissions or reclassifying preamendment class III device types; when asked for their time frame for doing so, the officials could not provide one

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GAO Report to Congress on Medical Devices Results cont.

- Between 2005 – 2007 FDA determined that relatively few class II & class III devices reviewed through the 510(k) process had new intended use or new technological characteristics.
- GAO estimated 1% had new intended use & 15% had new technological characteristics
- Among devices FDA determined SE * (& therefore cleared for marketing), all of the submissions had the same intended use and 86% had the same technological characteristics as a device already on the market
- In contrast, among the 248 510(k) submissions found NSE**, FDA determined that more than half had a new intended use or new technological characteristics

*SE (substantially equivalent) to predicate (prior) device

** NSE (not substantially equivalent) to predicate (prior) device

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GAO Report to Congress on Medical Devices Recommendations

- Recommendations:
- FDA expeditiously take steps to issue regulations for each class III device type currently allowed to enter the market through the 510(k) process

  Including:

  — (1) reclassifying each device type into a lower class or requiring it to remain in class III

  and

  — (2) for those device types remaining in class III, requiring approval for marketing through the PMA process

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 13. More than two decades after the Beagle voyages, Darwin published his seminal "Origins of the Species" rushing to print to beat similar, independent findings by fellow British naturalist and friend Alfred Russell Wallace.
- Darwin was not entirely pleased with his work, considering the 500+ page book to be an "abstract".
  - — He had envisioned something 5 times as long

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 14. Exactly 1,250 copies of "Origins" were printed in its first run
  - — All were distributed or sold within a day or so of publication, making the book an immediate best seller
- The book went through six editions during Darwin's lifetime.
  - — He made alterations and corrections in each one of them

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AE Reporting

- FDA Guidance for Clinical Investigators, Sponsors and IRB's
  - — Adverse Event Reporting to IRB's –

    Improving Human Subject Protection

    January 2009
- A "guidance document" that contains non-binding recommendations

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AE Reporting: The Problem

- Receipt of an increasingly large number of individual AE reports without analysis of their significance and often lacking context and detail rarely supports and in fact hinders an IRB's efforts to ensure human subject protection
- FDA regulations use different terms when referring to an *adverse event*
  - — *Adverse effect*: 21 CFR 312.64
  - — *Adverse experience*: 21 CFR 312.32
  - — *Unanticipated problem:* 21 CFR 312.66
  - — For devices, 21 CFR 812 uses *unanticipated adverse device effect*

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AE Reporting: Background

- After initial review/approval, IRB's are required to conduct continuing review
  - At intervals appropriate o the risk of the study, at least annually
  - Initial and continuing review' s primary purpose is "to assure the protection of the rights and welfare of the human subjects".
- To fulfill its obligations during the trial, an IRB must information concerning unanticipated problems involving risk to human subjects including adverse events considered unanticipated problems

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AE Reporting: Background

- Investigators are required to report promptly "to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately." 21CFR 312.64

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AE Reporting: Background

- Investigators are required to report promptly
  - "to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately." 21CFR 312.64
  - "to the IRB… all unanticipated problems involving risks to human subjects and others," including adverse events that should be considered unanticipated problems. 56.108(b); 312.53(c)(1)(vii) and 312.66

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AE Reporting: Background

- Sponsors are specifically required to notify all participating investigators and FDA (in a written IND report) of
  - "any adverse experience associated with the use of the drug that is both serious and unexpected"

    and
  - "any finding from tests in laboratory animals that suggests a significant risk for human subjects" 312.32(c)(1)(i)(A)(B)
- Sponsors are more generally required to
  - "keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug particularly with respect to adverse effects and safe use" 312.55(b)

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AE Reporting: Background

- Perhaps even more importantly, 312.32(c)(1)(i) requires a sponsor prepare an IND safety report to, among other thing, "analyze the significance of the adverse experience in light of previous, similar reports"

  and
- 312.32(b) requires the sponsor to "promptly review all the information relevant to the safety of the drug obtained or otherwise received by the sponsor form any source…"

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AE Reporting: Background

- Critical question for investigators:
  - What adverse events *should* be considered unanticipated problems that warrant reporting to IRB?

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 15. Herbert Spencer, a British philosopher and contemporary of Darwin, coined the phrase " survival of the fittest"
- Darwin adopted the tem in the 5th edition of "Origins", giving Spencer full credit

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 16. Darwin, a self taught zoologist, spent 8 years on the taxonomy of barnacles.

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AE Reporting: FDA Recommendation

- Only the following should be considered as *unanticipated problems* that must be reported to the IRB:
  - 1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury or Stevens-Johnson syndrome).

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AE Reporting: FDA Recommendation

- Only the following should be considered as *unanticipated problems* that must be reported to the IRB:
  - 2. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population e.g. tendon rupture, progressive multifocal leukoencephalopathy).

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AE Reporting: FDA Recommendation

- Only the following should be considered as *unanticipated problems* that must be reported to the IRB:
  - 3. Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AE's represents a signal that the AE's were not just isolated occurrences and involve risk to human subjects (rates in active higher than control groups).

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AE Reporting: FDA Recommendation

- Only the following should be considered as *unanticipated problems* that must be reported to the IRB:
  - 4. An AE that is described in IBD, protocol or CF but occurs at a specificity or severity that is inconsistent with prior observations. (e.g. elevated LFT's listed, hepatic necrosis observed

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AE Reporting: FDA Recommendation

- Only the following should be considered as *unanticipated problems* that must be reported to the IRB:
  - 5. A serious AE that is described or addressed in the IDB, protocol or CF, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence.

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AE Reporting: FDA Recommendation

- Only the following should be considered as *unanticipated problems* that must be reported to the IRB:
  - 6. A serious AE or other safety finding (animal, epidemiologic data etc.) that would cause the sponsor to modify IDB, study protocol or CF or would prompt other action by IRB to ensure protection of human subjects.

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 17. Darwin wrote 16 books, including a lengthy treatise on emotions in humans and other animals
  - He believed blushing to be a sign of deceit
- His last book, published in 1881, was " The Formation of the Vegetable Mold, Through the Action of Worms, With Observations on Their Habits".

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 18. After the Beagle voyages, Darwin never traveled far from his village home in England
- He was plagued by poor health and unexplained ailments whose symptoms, including headaches, heart palpitations, muscle spasms, pain, vomiting and vertigo, sent him to bed for months at a time
- Darwin pursued both traditional and novel medical treatments from dozens of doctors
  - He was a great believer in bath cures, but ot no lasting effect
- Numerous conditions have been blamed for Darwin's poor health including panic disorder and hypochondria
  - Many no suspect he suffered from Chagas disease
  - Darwin described how he was bitten by an insect now known to be a vector of the disease
- Darwin died of heart failure in 1882 at the age of 73.

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AE Reporting: Clinical Trials of Devices Under the IDE Regulations

- Unanticipated Adverse Device Effect (UADE): "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem to death was not previously identified in nature, severity or degree of incidence in the investigational plan or problem associated with a device that relates to the rights, safety, or welfare of subjects (21CFR 812.3(s).

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AE Reporting: Clinical Trials of Devices Under the IDE Regulations

- UADE's must be reported by investigator to sponsor and IRB:
  - As soon as possible, but in no event later than 10 working days after the investigator first learns of the event 812.150(a)(1).
  - Sponsors must immediately conduct an evaluation of a UADE and must report the results to FDA, all reviewing IRB's and investigators within 10 working days after the sponsor first receives the notice of the effect 812.46(b) & 812.150(b)(1).

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 19. Darwin ultimately considered himself to be an agnostic
- At the time of his death, a local evangelist insisted Darwin had renounced evolution and embraced Christianity
  - Darwin' family refuted the claim
- His last words, according to Emma, were 'I am not at the least afraid to die"

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Test Subjects Who Call the Scientist Mom or Dad

- Dr. Pawan Sinha, neuroscience prof. MIT
  - "Excited" about baby's birth
  - "because I really want to study him & do experiments with him" (strapped camera to head recording what baby looked at.
- Dr. Deborah Linebarger, directs Children's Media Lab U of Penn
  - "You need subjects and they're hard to get
  - Has involved all her 4 children in her studies of effects of media
- Dr. Arthur Toga, neurology professor UCLA
  - Has done brain MRI's on all three of his kids
- Dr. Stephan M. Camarata, prof. at Vanderbilt
  - Involved all his 7 kids in studies of learning & speech problems
- Dr. Deb Roy, prof. MIT
  - Imbedded 11 video cameras, 14 mics throughout house, recording 70% of son's first 3 years (250,000 hrs of tape)
  - "Human Speechome Project" (language development)

Pam Belluck, NYT 01/18/09 (page 1)

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Test Subjects Who Call the Scientist Mom or Dad

- IRB reporting
  - Some said "unnecessary" (no > risks than others)
  - Some said "involving your own kids proved risks were minimal"
  - Some signed CF's (some didn't) some had spouse sign
  - Dr. Gideon Deak told IRB subjects are a "sample of convenience", not random (but did not see need to specify they were his sons) ("I was only asking them questions, if it was a drug trial, that's different")

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Test Subjects Who Call the Scientist Mom or Dad

- Some consequences (cont.)
  - "fighting the natural feeling of wanting your kids to get the questions right"
  - One 5 yo answered "my parents don't listen to me and I sometimes feel lonely"
  - "my son needed more breaks than the other kids and wanted snacks"
  - After one twin outperformed another, researcher worried child was autistic". "I took only the good data, copied it & put it into both the babies books"
  - At 18 months old, after stating "No more questions Mama", on a walk, carried on Dad's back, Mom "tried to slip the questions in casually but child looked back with a smirk".

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Test Subjects Who Call the Scientist Mom or Dad

- Some consequences
  - "fighting the natural feeling of wanting your kids to get the questions right"
  - "my son needed more breaks than the other kids and wanted snacks"
  - After one twin outperformed another, researcher worried child was autistic". "I took only the good data, copied it & put it into both the babies books"
  - At 18 months old, after stating "No more questions Mama", later, on a walk, carried on Dad's back, Mom "tried to slip the questions in casually but she just looked back with a smirk".
  - By age 8 was falling sleep in MRI studies, but started out "claustrophobic in noisy scanner, with my head covered with a cage thing and body wrapped in tight blankets. The first time I just didn't stop talking".
  - "My wife was quite opposed….so it had to be done surreptitiously, like when she would go out or if I took him with me".

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200th Anniversary of Birth of Charles Darwin (February 12, 1809)

- 20. Darwin wanted to be buried without a fuss near his home
  - However, he received a state funeral

    One of only 5 such events not involving English royalty in the 19th century
- Among his pallbearers were Wallace and legendary naturalist-explorer Joseph Dalton Hooker and Thomas Huxley, both staunch defenders of his work
- He was buried at Westminster Abbey
  - Not far from the grave of Isaac Newton

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