Practicum on Clinical Trial Essentials for Dental, Oral, and Craniofacial Regenerative Technologies

William Giannobile, D.D.S., D.Med.Sc.
University of Michigan School of Dentistry
Dept. of Periodontics & Oral Medicine
January 31, 2019

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Goals of the Centers Towards Translation

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center
www.doctrc.com

C-DOCTOR
Center for Dental, Oral, & Craniofacial Tissue & Organ Regeneration
www.c-doctor.org

NIDCR-supported Resource Centers for developing Dental, Oral, Craniofacial Tissue Regeneration Consortium (DOCTRC) are a part of an initiative to **propel novel therapeutics from pre-clinical to FDA submissions to human clinical trials.**

This approach will **balance clinical needs** with technology and translational constraints to bring forward promising technologies.

… practicing clinicians, engineers, and scientists will come together with clinical dental practice, academia and industry leaders **to transform patient care.**

J. Dental Research, 97:361-363; 2018

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

PERSPECTIVE

REJUVENATING REGENERATIVE MEDICINE REGULATION

Rejuvenating Regenerative Medicine Regulation

R. Alta Charo, J.D., and Douglas Sipp, B.A.

New guidelines developed for regenerative medicine (RM) technologies based on recommendations by the International Society for Stem Cell Research. The FDA now considers cell and tissue-based product-specific guidance to imp
patients in human clinical trials given the r
technologies are coupled with surgica

Increased compliance measures for clinical cellular therapies for regeneration

N ENGL J MED 378;6 NEJM.ORG FEBRUARY 8, 2

The New England Journal of Medicine

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

ITP Program Overview

Project Entry/ Exit

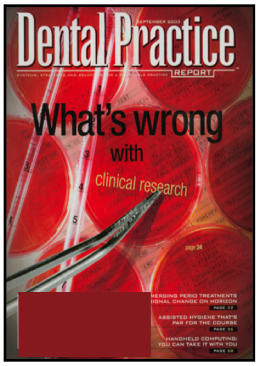
Stage 1 Discovery Conceptualization
Stage 2 Assessment
Stage 3 Testing Validation
Stage 4 Prototype manufacturing
Stage 5 Clinical Approval

RFPs UNMET NEEDS RCs
HIGH LEVEL ASSESSMENT
FULL PROPOSAL
QUANT. ASSESSMENT
FEEDBACK
ADVISORY TEAMS
DEVELOPMENT STRATEGY
TRAINING
PROJECT MGMT
PROGRESS REPORTING
STAGE III DOCTRC
Exit Clinical Trials

Successful outcomes of the Interdisciplinary Translational Project Program:
- Projects advancing to Q-Sub meetings, FDA IND/IDE, 510(k) submissions
- Clinical launch/initiation of clinical trials of an ITP technology
  - By ITP teams: Investigator-initiated studies
  - By external entities: Licensing to commercial entity
- Follow on funding for continued technology development
- NEWCO Formation

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Importance of Translational Research in Clinical Investigation

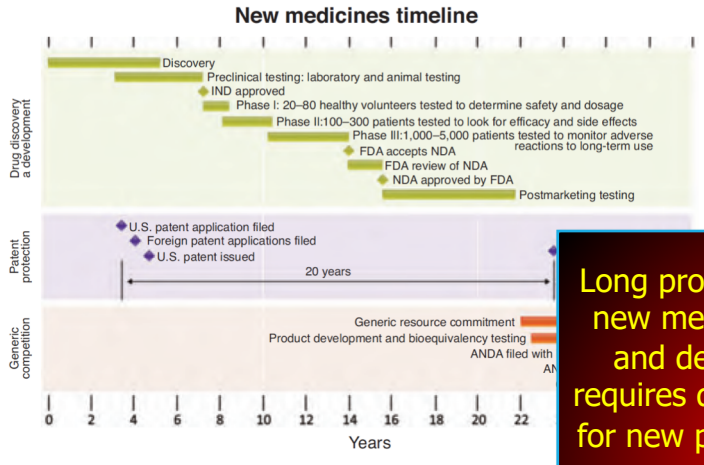


- Challenge in conversion of basic research to "chair-side or bed-side"
- Slow rate of new product development makes application to practice more difficult

Adapted from Lenfant, C. Clinical research to clinical practice - lost in translation? *N Engl J Med* 349: 868-874; 2003

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Clinical Development of Dental and Medical Products… *A Long Road*



Long process for new medicines and devices requires diligence for new products

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

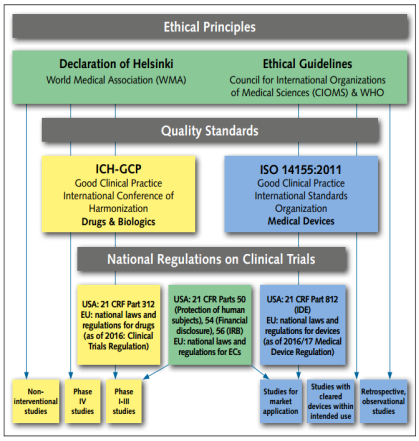
Regulations for Dental Drugs, Biologics and Devices

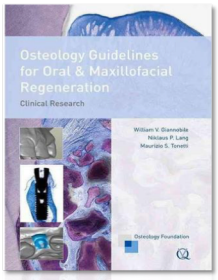
- Investigational new drugs
- Protection of human subjects
- Institutional review boards
- Good laboratory practices for non-clinical laboratory studies
- New drug applications
- Biologics
- Financial disclosure by clinical investigators
- Environmental impact considerations
- Labeling and advertising
- Current good manufacturing practices
- Devices and in vitro diagnostics
- Human tissues

Significant Responsibilities and Burdens for Solo Research Investigators

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Regulation of Patient-Oriented Research

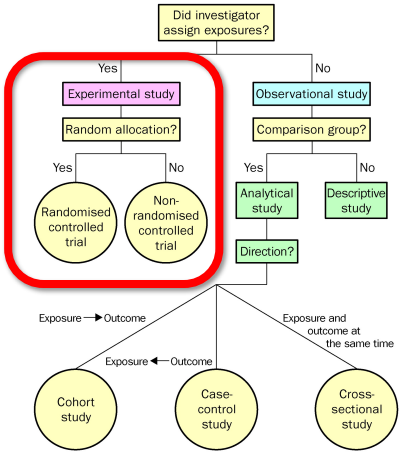


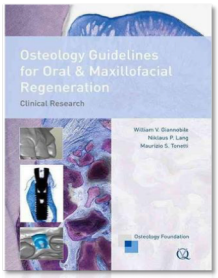


Denke G. Regulatory and Good Clinical Practice Aspects in Clinical Practice. In *Osteology Guidelines for Oral & Maxillofacial Regeneration Clinical Research* (2014), Giannobile WV, Lang NP, Tonetti MS, Editors. Quintessence Publishing, London, p. 12.

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Classification of Clinical Research Design

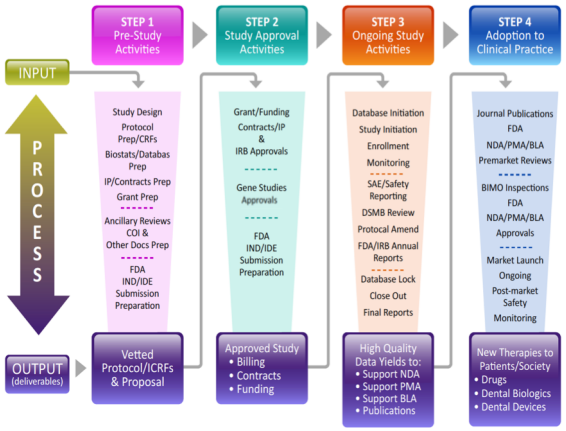




Grimes and Schulz, An overview of clinical research: the lay of the land. The Lancet 2002:359:57-61

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Clinical Research Process



From Kaigler D, Fuller K, Giannobile WV. Regulatory process for the evaluation of dental drugs, devices, and biologics. In *Clinical Research in Oral Health* (2010), Giannobile WV, Burt BA, Genco RJ, Editors. Wiley-Blackwell Publishers, New York.

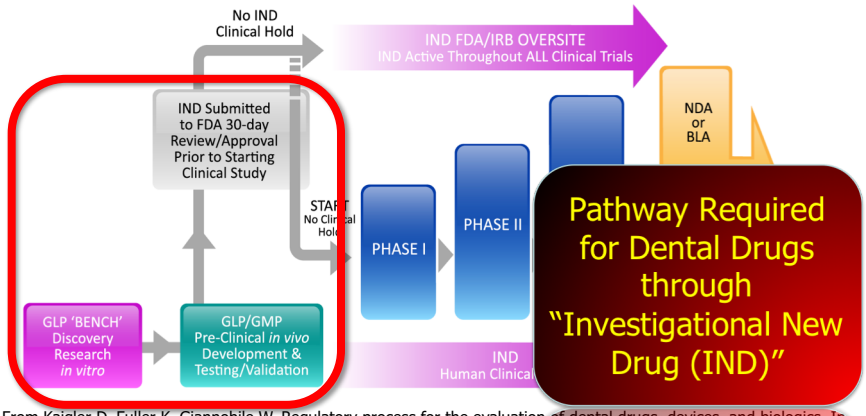
Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Phases of Human Clinical Trials

- **Phase I**: Small, dose escalation study that can include either patients or normal volunteers with the *primary goal to assess safety.*
- **Phase II:** One or more moderate size studies that are usually performed in patients and whose primary goal is to provide dosing requirements and preliminary evidence of efficacy and supplementary data on safety.
- **Phase III:** Large (usually multi-center) and are designed to show risk and benefit. There are designed to study safety and effectiveness data go support marketing approval and specific indications.
- **Phase IV:** Post-market approval for product's quality, safety, or effectiveness.

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

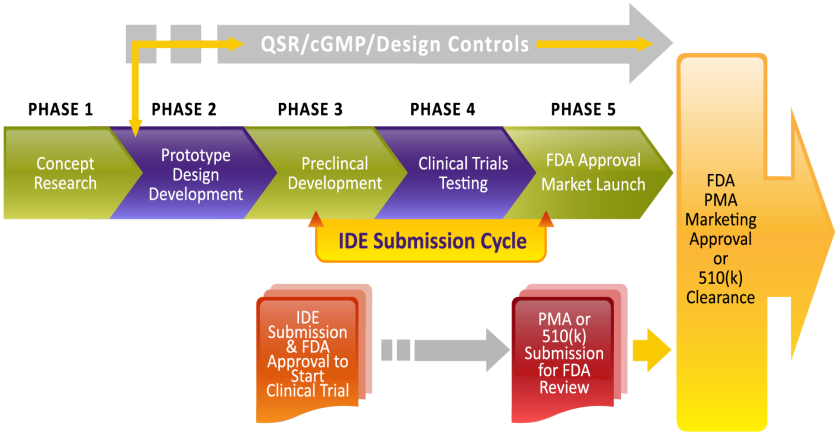
Drug and Biologics Life Cycle



From Kaigler D, Fuller K, Giannobile W. Regulatory process for the evaluation of dental drugs, devices, and biologics. In *Clinical Research in Oral Health* (2010), Giannobile W, Burt B, Genco R, Editors. Wiley-Blackwell Publishers, New York.

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Dental Device Development Life Cycle Overview that Require an Investigational Device Exemption (IDE)



From Kaigler D, Fuller K, Giannobile WV. Regulatory process for the evaluation of dental drugs, devices, and biologics. In *Clinical Research in Oral Health* (2010), Giannobile WV, Burt BA, Genco RJ, Editors. Wiley-Blackwell Publishers, New York.

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

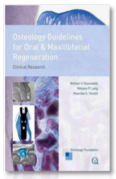
What is a Clinical Trial?

- A prospective study comparing the effect and value of intervention(s) against a control in human beings (Friedman et al)
- Not an idealized experiment: experimental units are humans (not identical and homogenous), interventions are not "exactly" reproducible, not all factors are controlled
- Purpose
  - Elucidate most appropriate treatment of future patients (Pocock 1983)
  - Necessary for licensing and labeling **of drugs, devices, dental procedures**
  - Improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease (Declaration of Helsinki)

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Clinical Development of Dental Drugs

Phase	Starting point	Most typical kind of study	Aspects of study	Study subjects
I	Initial administration of the investigational new drug in humans	Human pharmacology	• Estimation of initial safety and tolerability • Pharmacokinetics • Drug metabolism and drug interactions • Assessment of pharmacodynamics • Early measurement of drug activity	Mostly healthy volunteers
II	Initiation of studies with the primary objective to explore therapeutic efficacy in patients	Therapeutic exploratory	• Initial exploration of therapeutic efficacy in the targeted indication • Subsequent controlled trials to evaluate efficacy and safety • Surrogate endpoints or clinical endpoints • Homogenous study population • Dose finding for subsequent studies • Evaluation of possible endpoints, therapeutic regimens and target population for subsequent studies	Patients

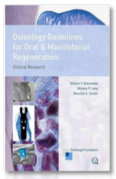


From Denke G. Regulatory and Good Clinical Practice Aspects in Clinical Practice. In *Osteology Guidelines for Oral & Maxillofacial Regeneration Clinical Research* (2014), Giannobile WV, Lang NP, Tonetti MS, Editors. Quintessence Publishing, London, p. 23.

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Clinical Development of Medical Devices

Phase	Starting point	Typical kind of study	Aspects of study
Exploratory	• Initiation of studies with the primary objective to explore effectiveness/performance and safety of the device in the intended use and in the target population	• Feasibility studies (uncontrolled) • Pilot studies (uncontrolled and/or controlled) • Sponsor-initiated	• Initial exploration of performance in the targeted indication • Subsequent controlled trials to evaluate effectiveness and safety • Surrogate endpoints or clinical endpoints • Homogenous study population • Evaluation of possible endpoints, application procedures and target population for subsequent studies
Confirmatory	• Initiation of studies with the primary objective to demonstrate/confirm therapeutic benefit of the use of the device	• Pivotal studies (mostly controlled) • Sponsor-initiated	• Confirmation of preliminary evidence accumulated in exploratory studies • Confirmation of safety and effectiveness in the intended indication and target population • Clinically meaningful endpoints • Basis for marketing approval/certification
Post-market clinical follow-up	• Marketing approval	• Therapeutic • Sponsor-initiated • Investigator-initiated	• Optimization of use • Health–economical aspects • Basis for maintenance of certification



Denke G. Regulatory and Good Clinical Practice Aspects in Clinical Practice. In *Osteology Guidelines for Oral & Maxillofacial Regeneration Clinical Research* (2014), Giannobile WV, Lang NP, Tonetti MS, Editors. Quintessence Publishing, London, p. 23.

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Choosing the Experimental Design

- Based on the aims and the outcome, a design can be identified.
- Other considerations
  - patient population
  - accrual limitations
  - previous experience with the treatment of interest in this or other populations
  - results from earlier phase studies
  - ethical issues
  - resources available

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

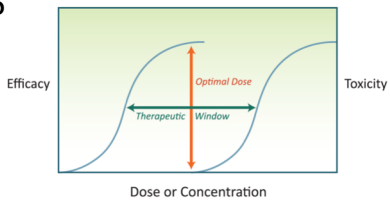
Phase I Clinical Trials

- Main Objective(s) and criteria for success
  - Phase I
    - How much toxicity am I willing to accept?
  - I think this drug has a dose effect curve
  - I think I will hit a Maximum Tolerated Dose (MTD)
  - I want to do my phase II as close to the MTD as possible
  - I don't want to expose more than
    - X patients to the MTD
    - Y patients to a very low dose

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Challenges in Considering a Phase I Study Design

- Phase I:
  - how many dose levels and why?
  - combination or single agent?
  - one or multiple disease types?
  - is expansion at MTD feasible?



Mitchell J, Park, G., Citron M., Pagano R., Wisner-Lynch L., Lynch SE (2010) . Phase I Clinical Trials. In *Clinical Research in Oral Health* (2010), Giannobile W, Burt B, Genco R, Editors. Wiley-Blackwell Publishers, New York.

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Phase II Study Design

- Provide initial assessment of efficacy or 'clinical activity'
  - **Screen out ineffective drugs**
  - **Identify promising new drugs for further evaluation**
- Further define safety and toxicity
  - **Type of dental drug or device**
  - **Frequency of dosing regimen**

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Phase II Study Design, Cont.

- Design:
  - Moderate patient population size (20-100)
  - Defined treatment and participant groups
  - Non-randomized vs. Randomized
  - Test of hypothesis
- Questions:
  - Efficacy clinically interesting?
  - Toxicity profile acceptable?
- Endpoints – response, toxicity, change in biomarkers, imaging, clinical measures

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Phase II Studies – Considerations in Design Choice

- What is historical control rate?
- Is a "reference arm" needed because the historical control healing is not well-defined (randomized phase II?)?
- Is there more than one schedule being considered? (randomized phase II?)?
- How well is safety profile defined?
- Safety vs. efficacy or both (Phase I/II designs)?

- Minimize cost of the trial
  - Minimize number of patients exposed to an ineffective treatment
  - Enroll as few patients as "necessary" to show benefit or failure

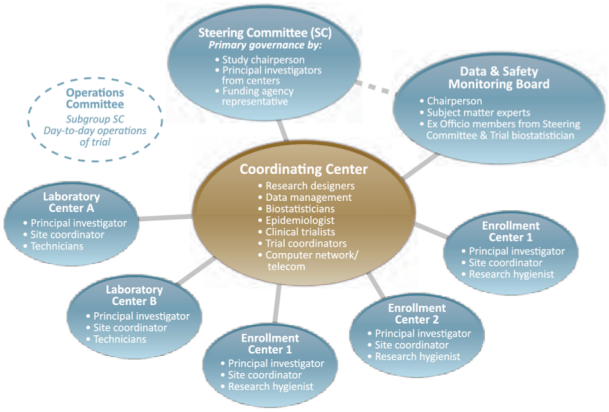
Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Phase III Clinical Trials

- Main Objective(s) and criteria for success
  - Phase III
    - What is "better"? (clinical utility)
  - How big an reparative effect do you expect to see?
    - Reduction of 10%? 20%? of whatever the control therapy is
    - What do you expect the control to be? (event rate 20%? 50%?)
    - How much power do you want to detect it? (80%? 90%?)
    - One or two sided? Conventional significance or other?

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Hypothetical Organization of a Phase III Clinical Trial



Braveman NS., Michalowicz BS (2010) . Phase III Pivotal Clinical Trials: Decision-making. In *Clinical Research in Oral Health* (2010), Giannobile W, Burt B, Genco R, Editors. Wiley-Blackwell Publishers, New York.

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

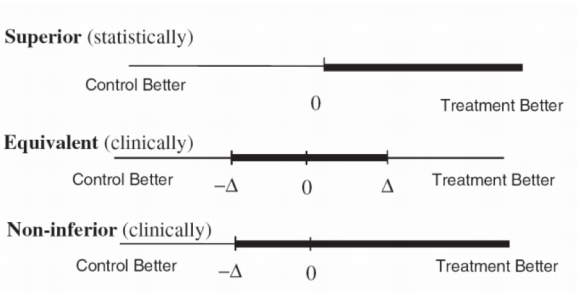
Types of Goals for Treatment Comparison

- **Superiority**: primary objective is to determine the magnitude of increased benefit of the novel intervention over standard therapy on effectiveness outcomes
- **Equivalence**: establish that a novel treatment is neither better nor worse (beyond a specified margin) than the standard
- **Non-inferiority**: establish that the novel intervention's effectiveness is not substantially less than the existing standard (generally to test treatments that have the primary benefit of decreased burden or harms relative to existing)

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Types of Goals for Treatment Comparison

- **Superiority:** better than
- **Equivalence**: equivalent to
- **Non-inferiority**: not notably worse than

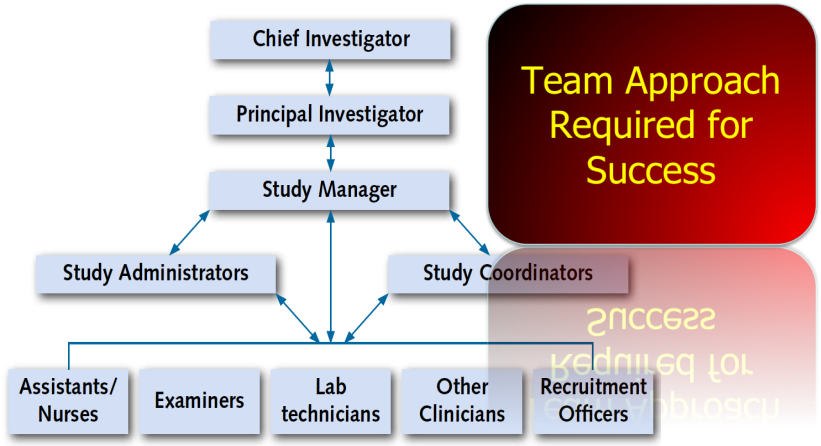


Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Analytical Plans depending on Study Goals

- Depends on the design and the goals of the human trial
- **Phase I**
  - often the analysis plan is descriptive
  - rare to see hypothesis testing (for primary aim)
- **Phase II**
  - Often estimation of treatment effect, summary of toxicity; comparison at higher α level
- **Phase III**
  - head to head comparison of two groups

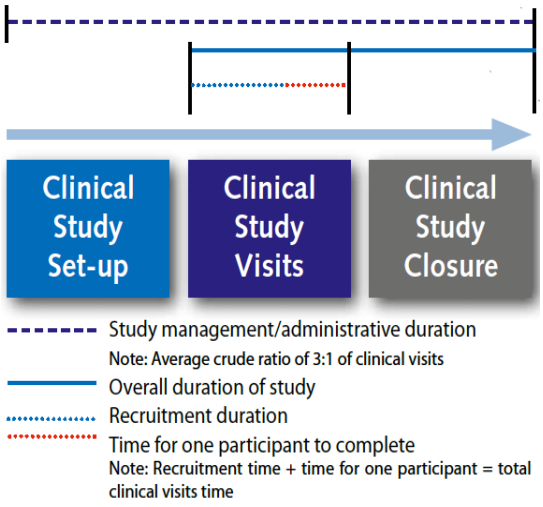
Clinical Study Team Framework



From Suvan J. Management of a clinical study. In *Osteology Guidelines for Oral and Maxillofacial Regeneration: Clinical Research* (2014), Giannobile WV, Tonetti M, Lang NP, Editors. Quintessence Publishers, Berlin.

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Clinical Study Initiation for Dental Investigation



Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Clinical Trial Monitoring

- Phase I/II trials
  - PI and local study team
  - External data & safety monitoring board (DSMB), sometimes NIDCR will assemble for NIH studies versus an external one demanded by the FDA
- Randomized phase III trials
  - Independent Data Safety Monitoring Committee
    - Other investigators
    - Statisticians (often includes the study stat)
    - Lay representatives
    - **NOT YOU, consider use of CROs**

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

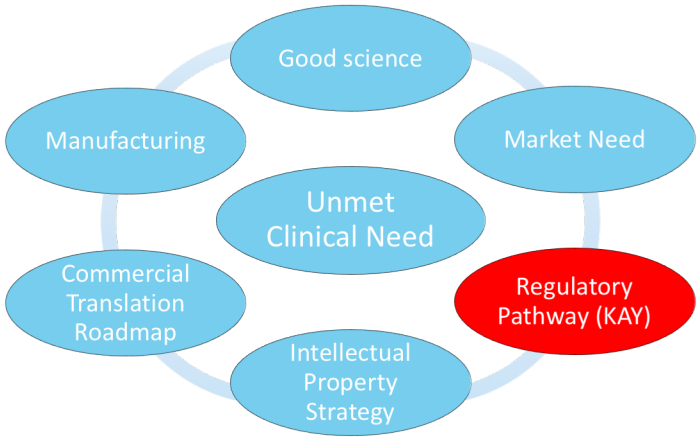
Clinical Trial Monitoring, Cont.

- Questions: Patient safety vs. Study integrity
  - Are there outside data that make this study no longer ethical?
  - Is accrual satisfactory to keep the study relevant?
  - Are there unexpected toxicities occurring?
  - Planned early and final looks
- Early stopping rules are generally built into studies
  - Stop because of huge benefit (O'Brien-Fleming)
  - Stop because of significant toxicity (DSMB)
  - Stop because of futility

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Clinical Translation

Besides good science, what else is needed to translate tissue engineering technologies?



Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Clinical and Market Expertise

MPWRM

Clinical Needs Advisory Board

McGuire Institute

- Practice based research network
- Determine and/or validate unmet clinical needs with TE/RM focus
- Access to established KOL to drive adoption in future

Thought-Leader Clinical Networks

- Dental Advisor™, Delta Dental

The Avenues Company

- DOC market experts
- Determine market acceptance criteria
- Identify hurdles to adoption and commercialization; match partners

Avenues

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

Resources and Acknowledgments

Clinical Research in Oral Health (2010). Giannobile WV, Burt B, Genco RJ, editors. Free access link: https://memberfiles.freewebs.com/17/70/79747017/documents/ClinicalResearchinOralHealth.pdf

Osteology Preclinical Research Guidelines (2011). Giannobile WV, Nevins M, Editors. Free access link: https://box.osteology.org/science/osteology-research-guidelines/pre-clinical-research-guidelines

Osteology Clinical Research Guidelines (2014). Giannobile WV, Tonetti M, Lang NP, editors. Free access link: https://box.osteology.org/science/osteology-research-guidelines/clinical-research-guidelines

Daniel Clauw, 2019 slides shared

Slides adapted from the Vail 2012 Methods in Clinical Cancer Research (Yu Shyr, Elizabeth Garrett-Mayer, Rick Chappell, Sue Hilsenbeck)

Michigan · Pittsburgh · Wyss
Regenerative Medicine Resource Center

A BIG THANKS TO…

CORPORATE SPONSORS, MPWRM RC MEMBERS & PARTNERS