Clinical Trials
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Clinical Research

• Medical research involving people
• Two types
  1. Observational Studies
  1. Clinical Trials
Observational Study

- Assesses health outcomes in groups of participants without assigning to particular intervention
- Example: Assess whether risk factor “R” predicts outcome after stem cell transplant
Clinical Trials

• Evaluates a medical, surgical, or behavioral intervention
  – Can be single arm (treatment only) or controlled (compared to SOC or placebo)
  – Goal is to assess safety and efficacy

• Example: Is new treatment “T” better than SOC at treating acute myeloid leukemia
## Phases of Drug Development

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<thead>
<tr>
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<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
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<tbody>
<tr>
<td><strong>No. of Participants</strong></td>
<td>15-30</td>
<td>&lt;100</td>
<td>100 to thousands</td>
<td>Several hundreds to several thousands</td>
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<tr>
<td><strong>Purpose</strong></td>
<td>First in humans</td>
<td>Determine efficacy</td>
<td>Compare new agent with standard treatment</td>
<td>Post–market Long-term safety and efficacy</td>
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<td>Find safe dose</td>
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Common aspects of trial design

- **Controlled**
  - Early phase studies are single arm (not controlled)
  - Controlled study needed to determine efficacy of treatment
  - May involve placebo
- **Randomized**
- **Blinded**
Key Players

• Investigators
  – Principal Investigator
  – Co-Investigators
• Research Nurse
• Research Coordinator
• Regulatory personnel
Are Clinical Trials Safe?

• **Highly Regulated**
  – Must follow established protocols and standards
  – International Conference on Harmonization Good Clinical Practice (GCP)

• **Multiple Layers of Protection**
  – Investigators/Site research Staff
  – Site Scientific Review
  – Institutional Review Board
  – Sponsor
  – Data Safety Monitoring Committee
  – FDA/EMA

• **Strict Adherence to Study Protocol**
• **Careful Monitoring and Reporting of Adverse Effects**
Why participate?

• No other reasonable treatment option

• Potential for better treatment
  – Efficacy and Side effects

• Contribute to knowledge of disease and advancement of care

• Access to therapy
What should you ask?

- What is standard of care?
- How does clinical trial differ from this?
- What are risks and benefits?
- Financial considerations
- Review consent form
Consent form - do’s and don'ts

Sign without reading consent

Read consent, get scared by side effects and decide not to participate

Review the consent AND ask clarifying questions
What should you NOT ask?

• Is this clinical trial better than standard care?
• Should I enroll in this clinical trial?
• Would you recommend this for your mom, dad, etc?
What happens after I sign consent?

- Screening
- Enrollment
- Assign to treatment
- Begin treatment
What happens while on treatment

- Trials may involve a one-time treatment or treatment over a period of time
- Regular visits
  - Assess for side effects
  - Assess response to treatment
When does study end?

• Treatment length
  – One time treatment
  – Time-limited treatment

• Treatment extensions
  – Open label
  – Crossover

• Follow-up
Participant Responsibilities

- Know when the study begins and ends.
- Show up at scheduled appointments on time
- Follow directions for proper use, dosing and storage of self-administered study medications
- Follow directions for providing samples, and preparing for tests, procedures or examinations.
- Follow directions regarding other medications and procedures.
- Inform if other medical care is needed
- Truthful answers to questions
- Inform the staff if there are questions you would rather not answer.
- Keep study confidential
- Inform of contact information changes.
- Follow withdrawal procedures
Example

Problem: Lack of HLA matched donor limits availability of allogeneic (donor) stem cell transplant
• Potential Solution: Use half-matched related donors
  – Parents, siblings, children
• Problem: Rejection, Graft v. Host Disease
• Cyclophosphamide given after transplant can allow grafts to take
  – Need high dose
  – Timing matters
  – Stem cells are resistant to it
Luznik, et al. BBMT 2008
A

Acute GVHD

Cumulative incidence (%)

Grades II-IV

Grades III-IV

Days after transplantation

B

Extensive chronic GVHD

Cy d 3 (Seattle; n=28)

Cy d 3.4 (Baltimore; n=40)

Days after transplantation

Luznik, et al. BBMT 2008
Passweg JR et al BMT 2021
Unmanipulated haploidentical in comparison

Comparable composite endpoints after

HLA-haploidentical vs matched unrelated donor transplants with posttransplant cyclophosphamide-based prophylaxis

Mahasweta Gooptu,1,2* Rizwan Romee,1,2* Andrew St. Martin,2 Mukta Arora,2 Monzr Al Malik,4 Joseph H. Antin,1 Christopher N. Bredeson,3,6 Claudio G. Brunstein,7 Saurabh Chhabra,8* Ephraim J. Fuchs,9 Nilanjana Ghosh,10 Michael R. Grunwald,10 Christopher G. Kanakry,11 Natasha Kekre,8* Jospeh P. McGurk,12 Ian K. McNiece,13 Rohtesh S. Mehta,14 Marco Mielcarek,15 Filippo Milano,16 Dipenkumar Modi,16 Ran Reshef,17,18 Scott R. Solomon,19 Mark A. Schroeder,20 Edmund K. Waller,21 Yoshiro Inamoto,15 Robert J. Soiffer,1 and Mary Eapen2
National Marrow Donor Program–Sponsored Multicenter, Phase II Trial of HLA-Mismatched Unrelated Donor Bone Marrow Transplantation Using Post-Transplant Cyclophosphamide

Bronwen E. Shaw, MD, PhD1; Antonio Martin Jimenez-Jimenez, MD, MS2; Linda J. Burns, MD1; Brent R. Logan, PhD1; Farhad Khimani, MD3; Brian C. Shaffer, MD4; Nirav N. Shah, MD5; Alisha Musseter, BS6; Xiao-Ying Tang, MPH3; John M. McCarty, MD7; Asif Alavi, MD8; Noshah Farhadfar, MD2; Katarzyna Jamieson, MD10; Nancy M. Hardy, MD11; Hannah Choe, MD12; Richard F. Ambinder, MD, PhD13; Claudio Anasetti, MD3; Miguel-Angel Perales, MD4; Stephen R. Spellman, MBS6; Alan Howard, PhD6; Krishna V. Komanduri, MD2; Leo Luznik, MD13; Maxim Norkin, MD, PhD14; Joseph A. Pidala, MD, PhD3; Voravit Ratanatharthorn, MD8; Dennis L. Confer, MD6; Steven M. Devine, MD6; Mary M. Horowitz, MD, MS1; and Javier Bolaños-Meade, MD13
BMT CTN 1703
Randomized, multicenter, Phase III trial

**Tacrolimus / Methotrexate** (n = 214)
- **Tacrolimus**: Initiate Day -3, goal blood level 5-15, begin taper after Day +90 is no active GVHD
- **Methotrexate**: 15 mg/m² on Day +1, 10 mg/m² on Days +3, +6, +11

**Post-transplant cyclophosphamide / Tacrolimus / Mycophenolate mofetil** (n = 214)
- **Post-transplant cyclophosphamide**: 50 mg/kg on Days +3 and +4
- **Tacrolimus**: Initiate Day +5, goal blood level 5-15, begin taper after Day +90 is no active GVHD
- **Mycophenolate mofetil**: Initiate Day +5 at 15 mg/kg/dose TID, stop Day +35 if no active GVHD

Eligible subjects receiving RIC allogeneic HCT (n = 428)
The Journey of Post-transplant Cyclophosphamide

Lab Research

Early Phase study in small population (Addressed Health Care Disparity)

Efficacy Confirmed in Observational Studies

Potential for use in all types of donor stem cell transplants
The Journey of Post-transplant Cyclophosphamide

Lab Research

Early Phase study in small population (Addressed Health Care Disparity)

Efficacy Confirmed in Observational Studies

Potential for use in all types of donor stem cell transplants

DISCLAIMER
• Clinical Research is highly regulated
• Both observational research and interventional studies offer valuable information
• May offer new or better treatment options
• Advances the knowledge and treatment of disease which leads to better medical care