Improving the Design Of Early Phase Stem Cell Clinical Trials

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Conflict of Interest Disclosure Statement

Asymmetrex, LLC
is a for-profit company
engaged in commercial development
related to ideas presented.

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Topics Addressed

- Discussion of the design features that currently limit the success of stem cell clinical trials
- The importance of quality sourcing and characterization of stem cell treatment preparations by suppliers
- Tension between FDA-authorized clinical trials and treatment evaluations in private stem cell clinics

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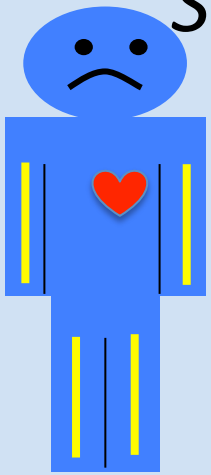
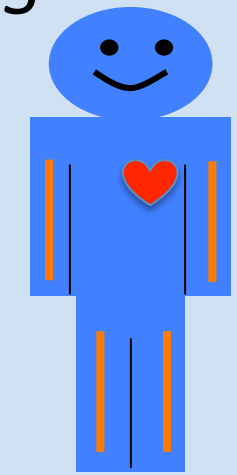
Stem Cell Clinical Trial Developments

The Established
Stem Cell Treatment Paradigm



Hematopoietic Stem Cells



SC DEFICIENCY
Inherited
Injury
Iatrogenic

TISSUE STEM CELLS
Homologous
Postnatal
Natural
Mobilized
Autologous
Allogeneic (Transport)
Perinatal (Cord Blood)
Uncultured

TREATMENT
Replacement
Durable
FDA-approved

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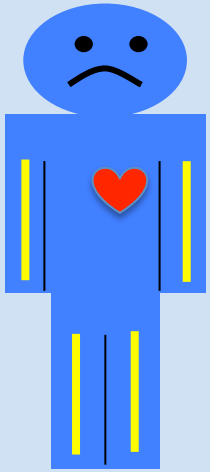
Stem Cell Clinical Trial Developments

Clinical Investigation – – – – *time* – – – → FDA INDs



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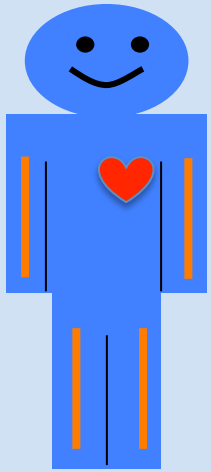

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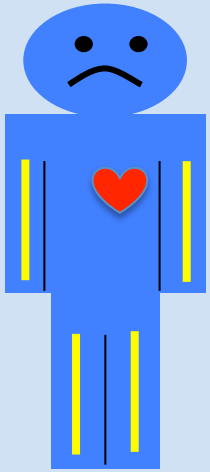
Stem Cell Clinical Trial Developments

100s of FDA-authorized Clinical Trials

Well-powered, Prospective, Double-blind, Randomized, Placebo-Controlled, Multicenter



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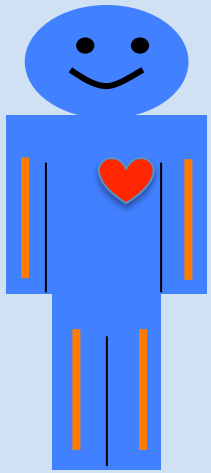

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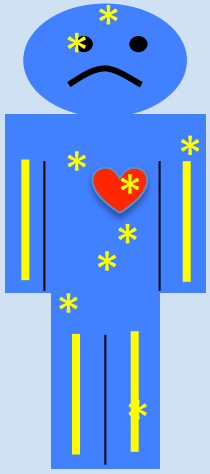
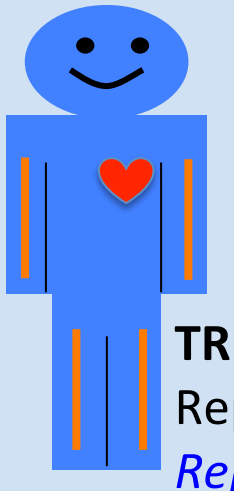
A New Stem Cell Clinical Trial Frontier



AILMENTS
Inherited
Injury
Iatrogenic
Cancer
Degenerations
Aging

STEM CELLS
Homologous
Non-homologous
Postnatal (*Multiple*)
Perinatal (*Multiple*)
Natural
Engineered (Gene Therapies)
Mobilized
Autologous
Allogeneic (***Transport***)
[Embryonic]
[Induced Pluripotent]
Uncultured
Expanded, Manufactured



TREATMENT
Replacement
Rejuvenation
Repair
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[Transient]
UNPROVEN

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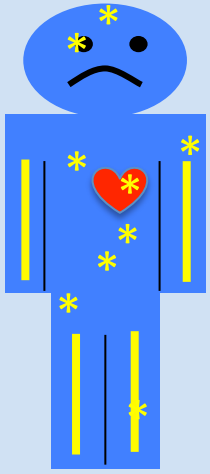
A New Stem Cell Clinical Trial Frontier



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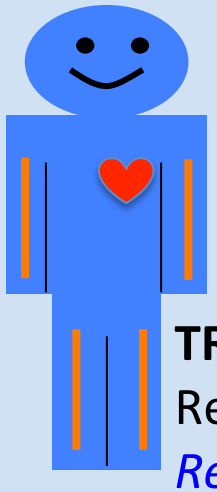
Uncultured
Expanded, Manufactured
HSCs – homologous replacement
– non-homologous rejuvenation
MSCs – non-homologous rejuvenation



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Discussion of the design features that currently limit the success of stem cell clinical trials

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Discussion of *the major unacknowledged design feature* that currently limits the success of ALL stem cell clinical trials

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Stem Cell Clinical Trial Design Goals

1. Relevant to the question evaluated
2. Feasible (e.g., supply)
3. Practical
4. Well-powered
5. Safe
6. Ethical
7. Manageable
8. Affordable
9. Yield interpretable findings

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The major limiting design feature?

1. Relevant to the question evaluated
2. Feasible (e.g., supply)
3. Practical
4. Well-powered
5. Safe
6. Ethical
7. Manageable
8. Affordable
9. ***Yield interpretable findings***

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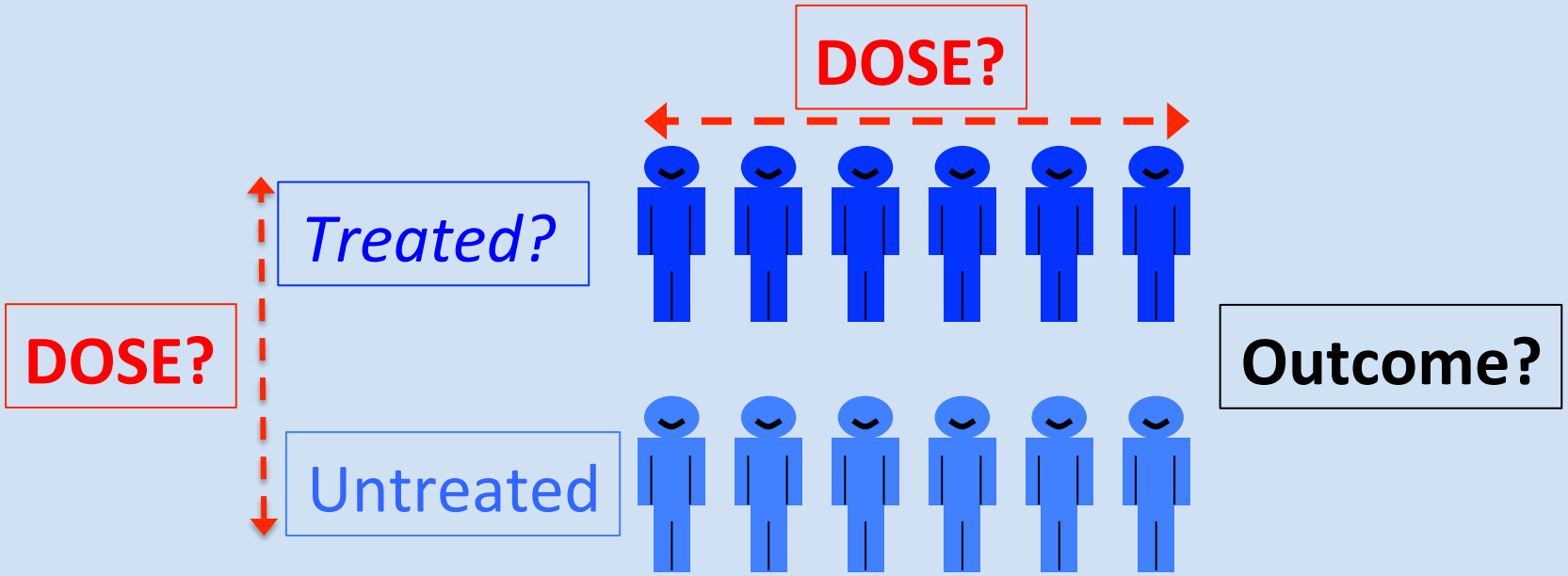
Stem Cell-Specific Dose

The major limiting design feature

- largely unacknowledged or unrecognized

*- previously, no technology available**



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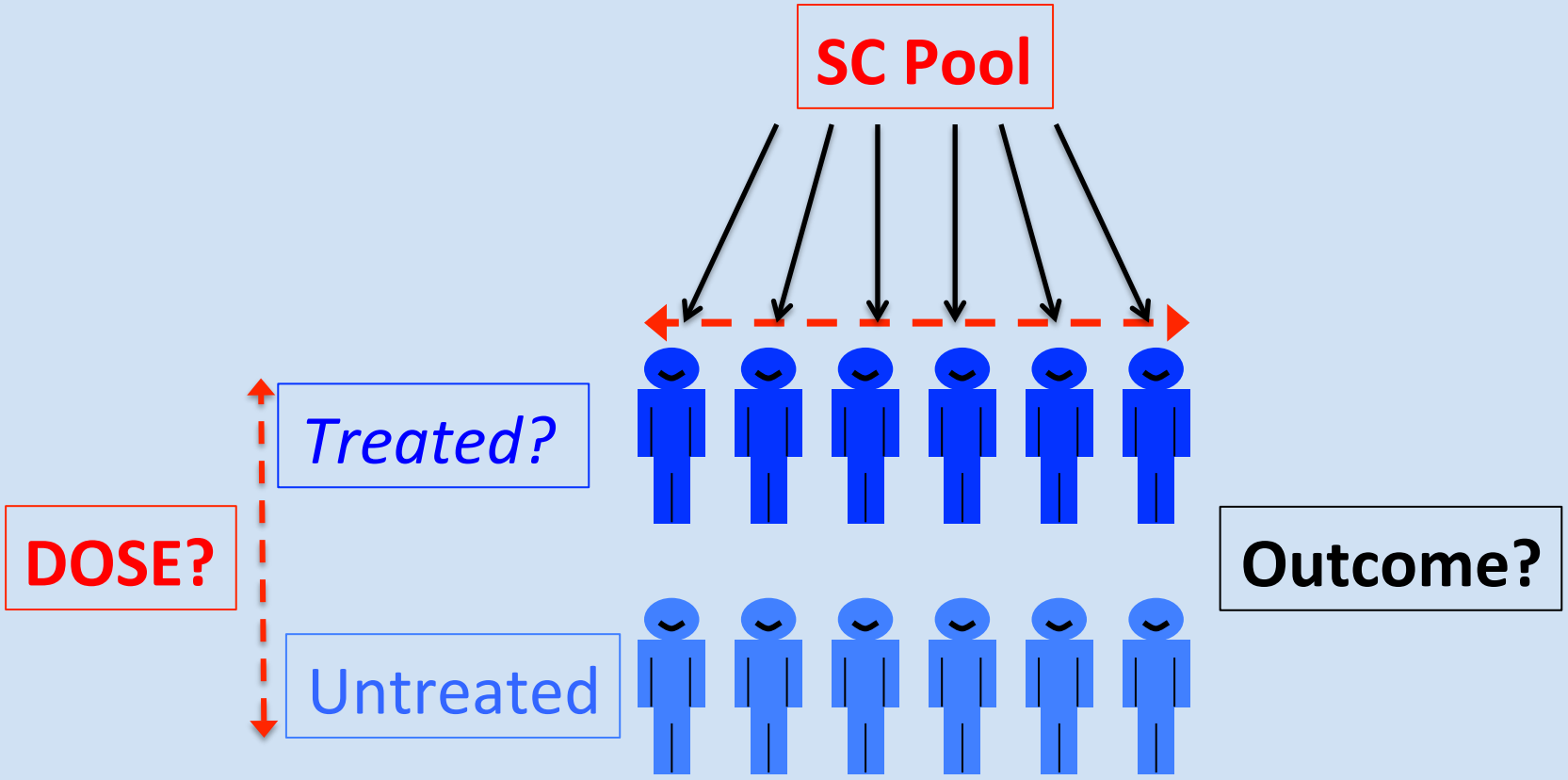
Stem Cell-Specific Dose

The major limiting design feature



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Stem Cell-Specific Dose

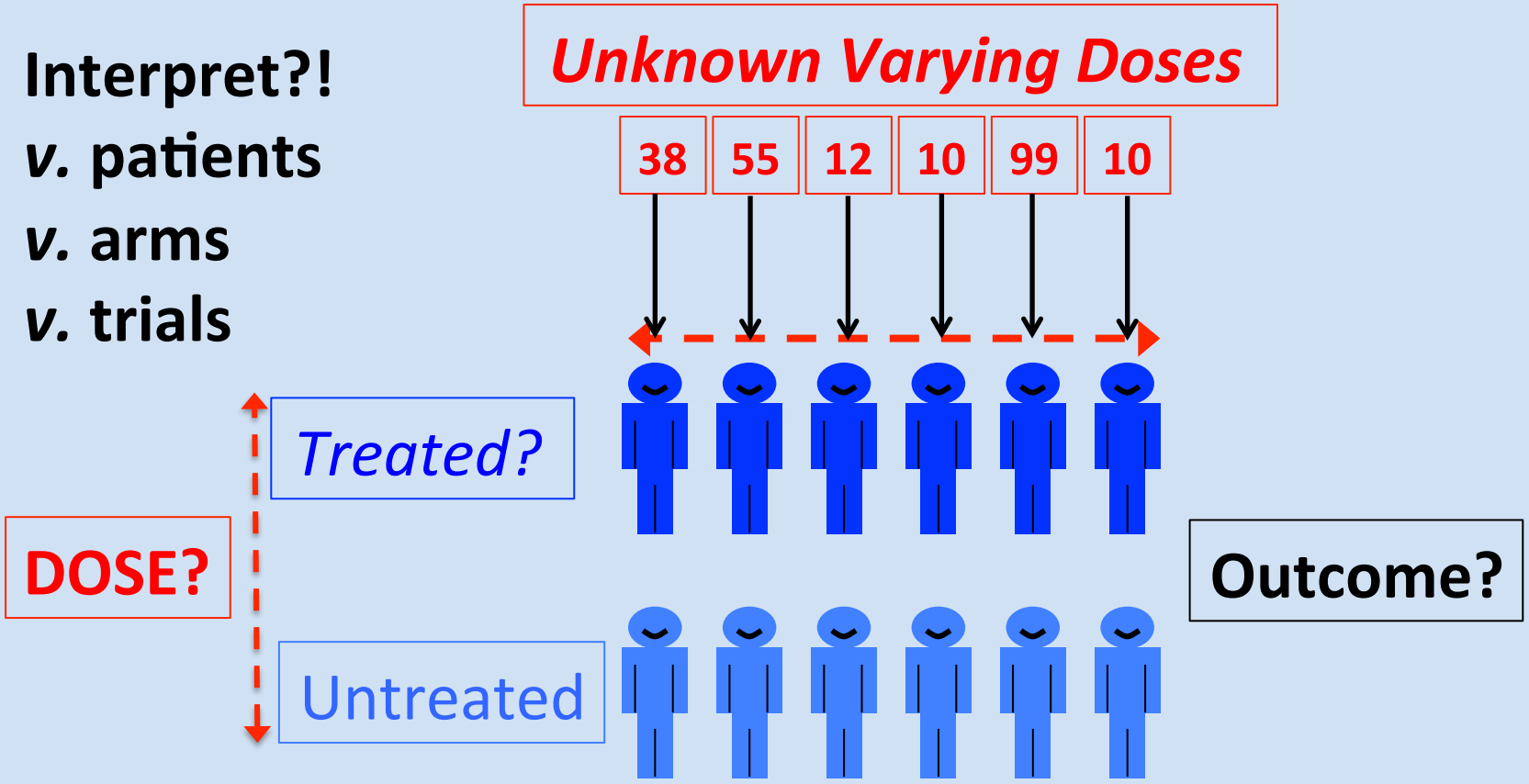
The major limiting design feature

Interpret?!

***v.* patients**

***v.* arms**

***v.* trials**



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In ALL Trials And Treatments Stem Cell-Specific Dose Is Unknown

I. Approved therapies and trials designed to improve
e.g., HSCT (cord blood, bone marrow, mobilized)

II. Cell replacement transplant trials
e.g., pancreas, liver, cornea

III. Non-homologous transplant tissue repair trials
e.g., MSC and HSC transplants for stroke, heart attack

IV. Gene therapy trials

V. Gene-editing therapeutics trials

VI. Treatments in private stem cell clinics

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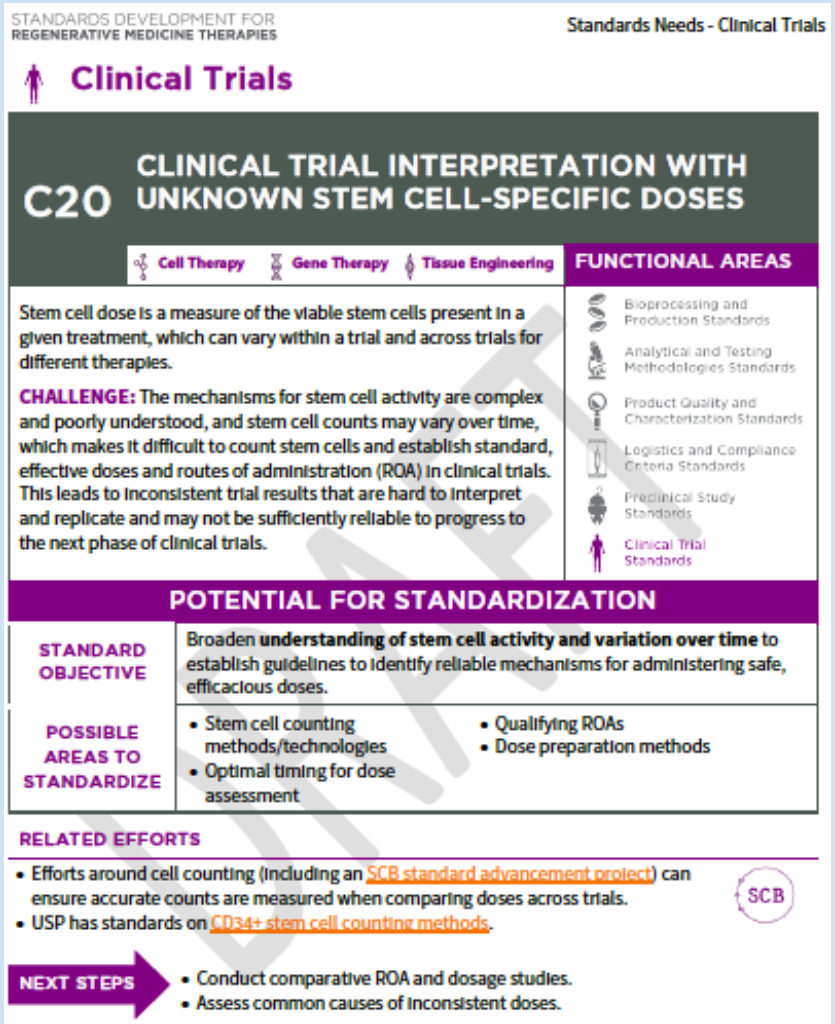
2019 FDA Standards Coordinating Body (SCB) Recognizes the Need



STANDARDS DEVELOPMENT FOR
REGENERATIVE MEDICINE THERAPIES

Standards Needs - Clinical Trials

Clinical Trials

C20 CLINICAL TRIAL INTERPRETATION WITH UNKNOWN STEM CELL-SPECIFIC DOSES

Cell Therapy | Gene Therapy | Tissue Engineering

Stem cell dose is a measure of the viable stem cells present in a given treatment, which can vary within a trial and across trials for different therapies.

CHALLENGE: The mechanisms for stem cell activity are complex and poorly understood, and stem cell counts may vary over time, which makes it difficult to count stem cells and establish standard, effective doses and routes of administration (ROA) in clinical trials. This leads to inconsistent trial results that are hard to interpret and replicate and may not be sufficiently reliable to progress to the next phase of clinical trials.

FUNCTIONAL AREAS

- Bioprocessing and Production Standards
- Analytical and Testing Methodologies Standards
- Product Quality and Characterization Standards
- Logistics and Compliance Criteria Standards
- Preclinical Study Standards
- Clinical Trial Standards

POTENTIAL FOR STANDARDIZATION

STANDARD OBJECTIVE	Broaden **understanding of stem cell activity and variation over time** to establish guidelines to identify reliable mechanisms for administering safe, efficacious doses.
POSSIBLE AREAS TO STANDARDIZE	• Stem cell counting methods/technologies • Optimal timing for dose assessment • Qualifying ROAs • Dose preparation methods

RELATED EFFORTS

- Efforts around cell counting (including an SCB standard advancement project) can ensure accurate counts are measured when comparing doses across trials.
- USP has standards on CD34+ stem cell counting methods.

SCB

NEXT STEPS

- Conduct comparative ROA and dosage studies.
- Assess common causes of inconsistent doses.

DRAFT

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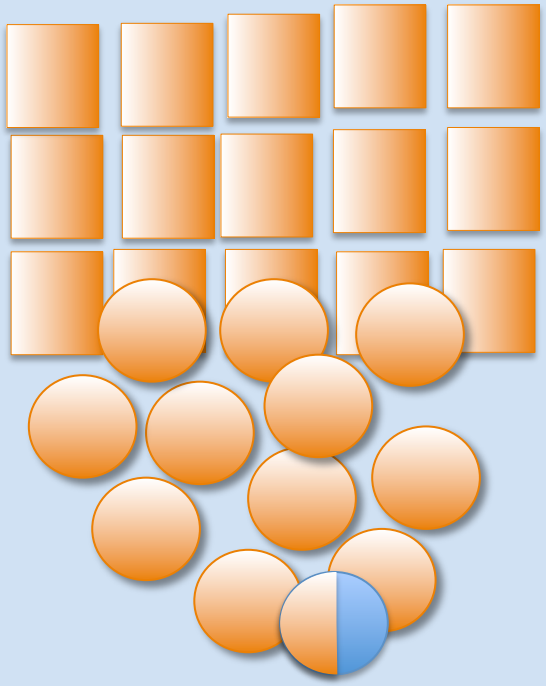
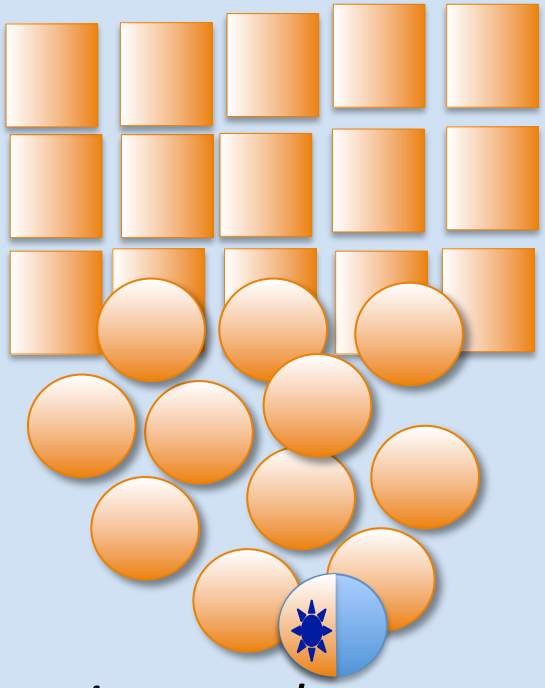
Previously, adult tissue stem cell counting has been unavailable because…



1. Adult tissue stem cells are a small fraction of total tissue cells, even after best isolation (< 1% or less).



2. No misnamed "stem cell biomarkers" distinguish adult tissue stem cells from committed progenitor cells.

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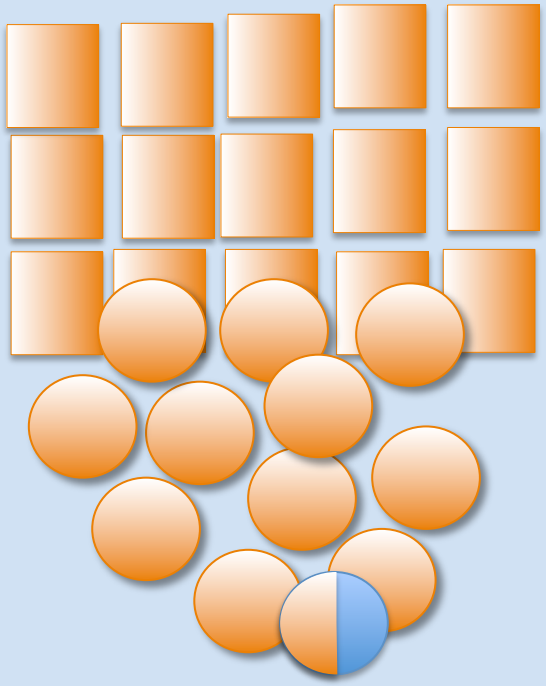

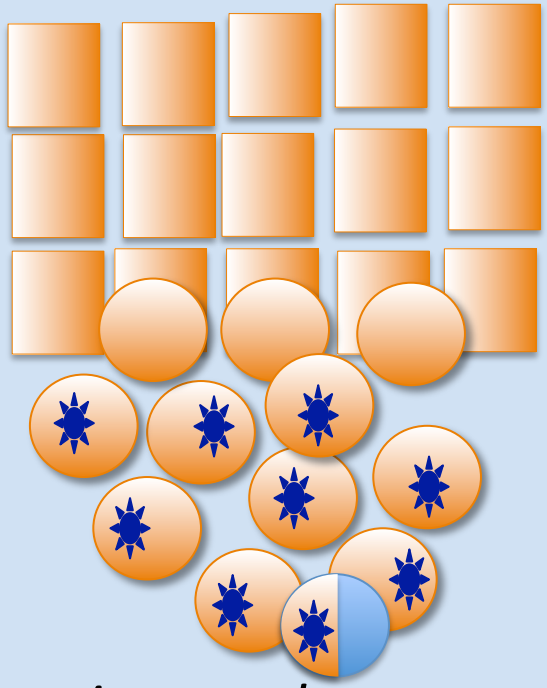

CD34
CD133
CD90

1. Adult tissue stem cells are a small fraction of total tissue cells, even after best isolation (< 1% or less).

2. No misnamed "stem cell biomarkers" distinguish adult tissue stem cells from committed progenitor cells.

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The importance of quality sourcing and characterization of stem cell treatment preparations by suppliers

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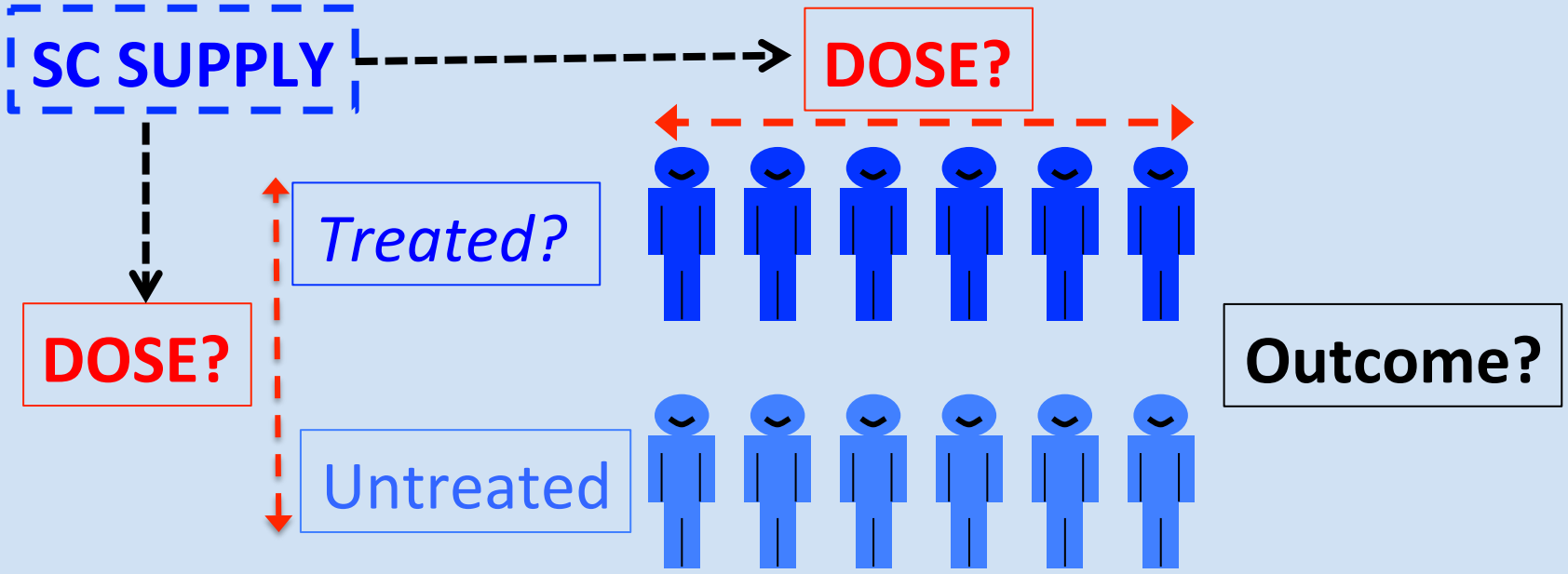
Stem Cell-Specific Dose

Overlooked factor for quality supply

- *largely unacknowledged or unrecognized*
- *previously, no technology available**



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Stem Cell Supply Quality Goals

Currently Undermined by Need for SC counting

1. cGMP
2. Sterility
3. Xeno-free
4. Affordable
5. ***Viability – stem cell-specific***
6. ***Potency – dose?***
7. ***Quantity – stem cell-specific***
8. ***Reproducibility – dose?***
9. ***Transport stability – stem cell-specific***

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Tension between FDA-authorized clinical trials and treatment evaluations in private stem cell clinics

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FDA-Authorized Stem Cell Clinical Trials

HCT/Ps – Human cell and tissue products guidances

Tissue Stem Cells (HSCs, MSCs, etc.)

Clinical Trials	**Safety!**
Conventional approval	**Efficacy?**
IND	
NDA	
PMA	
100s trials	
est. 30,000 patients	

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FDA-Authorized Stem Cell Clinical Trials vs. Private Stem Cell Clinic Treatments

HCT/Ps – Human cell and tissue products guidances

Tissue Stem Cells (HSCs, MSCs, etc.)

Clinical Trials	**Safety!**	**Stem Cell Clinics**
Conventional approval	**Efficacy?**	*Non-approved*
IND		FDA oversight?
NDA		*Recent FDA Scrutiny*
PMA		
100s trials		> 500 US clinics
est. 30,000 patients		***est. >250,000 patients***

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FDA-Authorized Stem Cell Clinical Trials vs. Private Stem Cell Clinic Treatments

2018 HCT/Ps – New Guidances

Tissue Stem Cells (HSCs, MSCs, etc.)

351 Guidance	**361 Guidance**
Non-homologous use?	Homologous use?
Manipulated?	Minimally manipulated?
Requires IND Approval	***Exempt, BLA register only***

Biological rationales – illogical, inconsistent, contrived

Patient protection goals – health and financial

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FDA-Authorized Stem Cell Clinical Trials vs. Private Stem Cell Clinic Treatments

HCT/Ps – Human cell and tissue products guidances

Tissue Stem Cells (HSCs, MSCs, etc.)

Clinical Trials	**Safety!**	**Stem Cell Clinics**
Conventional approval	**Efficacy?**	*Non-approved*

Both improve for patients and stem cell medical progress when tissue stem cell-specific counting and dosing are finally implemented.

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