Policy for Scientific Review of Clinical Protocols Utilizing the NIH Clinical Center

Clinical Center Research Hospital Board
July 14, 2017

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Chief Scientific Officer, NIH Clinical Center
NIH Associate Director for Clinical Research
Outline

• Scientific Review of Clinical Protocols

• Prioritization of Protocols Using Scarce Resources at the CC
## Total Clinical Protocols in Intramural Program: 2171

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical Center</th>
<th>Off site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1636</td>
<td>535</td>
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<tr>
<td>Interventional Clinical trials</td>
<td>800</td>
<td>52</td>
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<tr>
<td>Phase 1</td>
<td>268</td>
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<tr>
<td>Phase 2</td>
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<td>Phase 3</td>
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<td>9</td>
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<td>Phase 4</td>
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<td>5</td>
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<td>Natural History</td>
<td>740</td>
<td>471</td>
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<td>Training</td>
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<td>Screening</td>
<td>69</td>
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</table>

* FY 2016 data Provided by Kim Mitchell, Office of Protocol Services, CC
Scientific Review Policy for Clinical Protocols

• Describes minimum requirements for Institute/Center (IC) scientific review of IRP clinical protocols.
• Policy includes prioritization of protocols across ICs that use scarce resources.
• Scientific review will be completed before IRB review.
A standard IT tool will be used for protocol authoring with defined templates for writing protocol (OHSRP, Regulatory, Scientific Review, IRB Review requirements).

Initially templates a “word” type document currently available.

Long term need a relational data base to maximize benefit of protocol authoring tool. Currently does not exist.
Scientific Review Policy for Clinical Protocols cont.

Scientific reviews include:

1. Concept review (lab/branch/SD level at IC discretion)

2. Initial review of complete protocol (scientific review committee with CD/SD oversight; may include extramural reviewers).

3. Ongoing reviews (annual, and quadrennial).
   - Annual - by Lab/Branch at time of IRB review
   - Quadrennial - in depth review (extramural reviewers).
     (Still right study? Still right group? Are best methods being used? Should it be continued?)
Due to scarce resources at the CC not all protocols receiving outstanding scientific review can be implemented promptly.

- Process has been largely “first come first serve.”
- We can’t do everything.
- Some protocols already not being done or being done slowly.

Therefore, the scientific review policy includes a process for prioritization of protocols that use scarce resources and to make decisions more deliberate than random.
What is a Scarce Resource at the CC?

Demand and need are present, with limited resource available.
Scarce Resources at the Clinical Center

• Cell processing; apheresis services
• Imaging (MRI/MRI PET/CT)
• Research PET-scan slots; availability of new radiotracers
• Bone marrow/stem cell transplantation
• Operating rooms
• Metabolic chambers

Multi-modality minimally invasive procedural suite

Metabolic chamber
Scarce Resources at the Clinical Center-cont.

- Drug compounding-sterile and nonsterile
- Drug pharmacokinetics/pharmacodynamics
- Microbiology testing of sterile products
- Special testing in lab medicine
- Pediatrics-deep sedation for procedures
- Biomechanics lab
Cell Processing in Department of Transfusion Medicine as Pilot for Prioritization
IC Utilization of Cell Processing Services FY16

- NHLBI, $1,637,242
- NIAID, $897,278
- NINDS, $61,352
- NIDDK, $34,649
- NCI, $3,435,985
- CC, $30,819
Change in Number of IND Cell Processing Protocols in DTM 2012-2017

Number of Protocols Opening and Closing Each Year

Accumulative Change in Protocol Number
Cell Processing Activity

Department of Transfusion Medicine CC

• 37 protocols currently being implemented
  o 5 Complex Hematopoietic Stem Cell (HSC) Transplants
  o 18 Complex Cell and Gene Therapy
    (13 complex protocols in queue because lack of tissue culture rooms)
    o 14 Minimally manipulated HSC for transplants

• 8 new protocols currently in product development (2 per quarter)

• 20 projected future protocols identified by ICs (March 2017)
  o 1 ready 2017
  o 7 ready 2018
  o 2 ready 2019
  o 10 ready 2020
Surgery Branch, NCI

• 8 Complex protocols currently active

• 15 Projected to be active in 2020
Cell Processing Limiting Resources

Space (rooms)

Staff
Cell Processing Capacity: Space/Rooms

- **3T (current space)**
  - 4 rooms for complex IND products
  - 1 room for “standard of care transplants”, minimal manipulation

- **3 W (Surgery Branch, NCI)**
  - 1 room (currently operational)

- **2J (Projected available Nov. 2017)**
  - 7 rooms
  - *Note: when 2J opens 3T closes for 6 mo renovation*

- **Trailers for NCI**
  - 2 rooms (functional Nov. 2017)

- **Modular**
  - 3 rooms for NCI Surgery (Nov. 2018)
  - 3 rooms for DTM (Feb. 2019)

- **E wing 12th floor old CC (Projected 2021)**
  - 7 rooms
Cell Processing Capacity: Staff

Dept of Transfusion Medicine
30 staff manage 37 protocols today
• 12 additional staff needed for 13 protocols currently in queue

Surgery Branch, NCI
12 staff manage 8 protocols today
• 7 additional staff needed for 7 additional protocols in 2020

PROBLEM: Space and staff constraints.
We need to prioritize cell processing protocols today.
Rationale for Prioritization

• To assure the most compelling protocols being performed

• To identify shortages in scarce resources that will inform discussion as to future investments to assure the CC remains vibrant.
Principles of Prioritization

• **Fair**
  - Transparent
  - Mechanism to resolve disputes
  - Inclusiveness of stakeholders
    - Those involved in funding decisions
    - Parties in charge of delivering the resource/service
    - Representatives of potential beneficiaries of the research (patients)

• **Clinical protocols address important scientific questions**

• **Assure optimal use of the Clinical Center**

• **Flexible**
  - The priority setting process should be adjustable to promote acceptability and feasibility.

• **Develop outcome measures to evaluate success of process**
  - Stakeholders believe process is fair
  - Priorities chosen based on clear rationale
Prioritization Process

1. Process overseen by subcommittee of IC Directors and chaired by ADCR/CSO CC.
IC Directors Subcommittee on Protocol Prioritization

Diana Bianchi (NICHD)
Josie Briggs (NCCIH)
Anthony Fauci (NIAID)- Hugh Auchincloss Substituting
Walter Koroshetz (NINDS)
Doug Lowy (NCI)
Roderic Pettigrew (NIBIB)
Paul Sieving (NEI)

John Gallin (CSO CC, NIH ADCR), Chair
Prioritization Process cont.

2. Requires batching of all protocols and prioritizing of new and active (ethical considerations for active protocols).

3. Early career investigators and new IC users of scarce resource receive special consideration.

4. CDs do initial prioritization within their IC then harmonize across ICs with other CDs using a new prioritization tool.
5. Responsible CC dept. works with CDs to identify how far down list capacity allows. (Early career PI, new user ICs get special consideration).

6. ICs encouraged to identify alternative off-site locations for protocols not accommodated.

7. Subcommittee of IC Directors adjudicates issues and makes recommendations for increase (or decrease) investment in a scarce resource.
Prioritization of Protocols
<table>
<thead>
<tr>
<th>#</th>
<th>Protocol #</th>
<th>Protocol Title</th>
<th>Institute/ Center</th>
<th>Expected Completion Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10-H-0154</td>
<td>Allogeneic hematopoietic stem cell transplantation for severe aplastic anemia and other bone marrow failure syndromes using G-CSF mobilized CD34+ selected hematopoietic precursor cells co-infused with a reduced dose of non-mobilized donor T-cells</td>
<td>NHLBI</td>
<td>2019</td>
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<tr>
<td>2</td>
<td>N/A</td>
<td>Autologous Cell Therapy for Age-Related Macular Degeneration Using Patient-Specific Induced Pluripotent Stem (iPS) Cells</td>
<td>NEI</td>
<td>2020</td>
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<tr>
<td>3</td>
<td>N/A</td>
<td>TSLPR-CAR T cells to treat B cell leukemia</td>
<td>NCI</td>
<td>2021</td>
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<tr>
<td>4</td>
<td>10-C-0054*</td>
<td>Administration of Anti-CD19-Chimeric-Antigen-Receptor-Transduced T Cells from the Original Transplant Donor to Patients with Recurrent or Persistent B-Cell Malignancies After Allogeneic Stem Cell Transplantation (Stem Memory T cells)</td>
<td>NHLBI</td>
<td>2019</td>
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<tr>
<td>5</td>
<td>14-C-0168*</td>
<td>A Phase I Clinical Trial of T Cells Targeting B-Cell Maturation Antigen for Previously Treated Multiple Myeloma</td>
<td>NCI</td>
<td>2018</td>
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<tr>
<td>6</td>
<td>16-C-0054*</td>
<td>T Cells Expressing a fully-human anti-CD19 Chimeric Antigen Receptor for treating B-cell malignancies</td>
<td>NCI</td>
<td>2018</td>
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<tr>
<td>7</td>
<td>16-C-0163*</td>
<td>A Randomized Phase I/II Trial of T Cell Receptor Gene Therapy Targeting HPV-16 E7 with or without PD-1 Blockade for HPV-Associated Cancers</td>
<td>NCI</td>
<td>2018</td>
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<tr>
<td>8</td>
<td>17-C-0048*</td>
<td>T Cells expressing a fully-human anti-CD30 Chimeric Antigen Receptor for treating CD30-expressing lymphomas</td>
<td>NCI</td>
<td>2019</td>
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<td>9</td>
<td>N/A</td>
<td>A Randomized Phase I/II Trial of T Cell Receptor Gene Therapy Targeting HPV-16 E6</td>
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<td>2018</td>
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<td>10</td>
<td>15-C-0029*</td>
<td>Phase I Dose Escalation Study of Anti-CD22 Chimeric Receptor T Cells in Pediatric and Young Adults with Recurrent or Refractory CD22-expressing B Cell Malignancies</td>
<td>NCI</td>
<td>2019</td>
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<td>N/A</td>
<td>CD19/CD22 Bi-specific CAR T cells</td>
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<td>12</td>
<td>N/A</td>
<td>Gene correction of Leukocyte Adhesion Deficiency (LAD) CD18 CD34+ cells</td>
<td>NHLBI</td>
<td>2020</td>
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<tr>
<td>13</td>
<td>16-N-0072*</td>
<td>A Pilot Study of Adoptive Cellular Immunotherapy for Progressive Multifocal Leuкоencephalopathy with Ex Vivo Generated Polyomavirus-Specific T-cells PyVST for PML</td>
<td>NINDS</td>
<td>2021</td>
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<tr>
<td>14</td>
<td>11-C-0016</td>
<td>Rapamycin-Resistant T Cell Therapy of Multiple Myeloma: Relapse Prevention and Relapse Therapy,*</td>
<td>NCI</td>
<td>2017</td>
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<tr>
<td>15</td>
<td>17-C-0011*</td>
<td>Phase 1 Study of intrapentoneal infusion of autologous monocytes with Sylatron (Peginterfero alfa-b) and Actimmune (Interferon gamma 1b) in women with recurrent or refractory ovarian cancer, fallopian tube cancer or primary peritoneal cancer</td>
<td>NCI</td>
<td>2020</td>
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<tr>
<td>16</td>
<td>08-H-0186*</td>
<td>Safety and the anti-tumor effects of escalating doses of adoptively infused ex vivo expanded autologous natural killer (NK) cells against metastatic cancers or hematological malignancies sensitized to NK–TÂAIL cytotoxicity with Bortezomib</td>
<td>NHLBI</td>
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<tr>
<td>17</td>
<td>14-C-0182*</td>
<td>Phase I/II Trial of Early Infusion of Multivirus Specific T cell (MVST) to Prevent Post Transplant Viral Infections</td>
<td>NHLBI</td>
<td>2017</td>
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<tr>
<td>18</td>
<td>08-H-0046</td>
<td>Co-Infusion of umbilical cord blood and haploidentical CD34+ cells following nonmyeloablative conditioning as treatment for severe aplastic anemia and MDS associated with severe neutropaenia refractory to immunosuppressive therapy</td>
<td>NHLBI</td>
<td>2017</td>
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<tr>
<td>19</td>
<td>13-H-0144</td>
<td>Peripheral blood stem cell allotransplantation for hematological malignancies using ex vivo CD34 selection – a platform for adoptive cellular therapies.</td>
<td>NHLBI</td>
<td>2018</td>
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<tr>
<td>20</td>
<td>14-H-0180</td>
<td>Ultra Low dose IL-2 Therapy as GVHD Prophylaxis in Haploidentic Stem Cell Transplantation</td>
<td>NHLBI</td>
<td>2017</td>
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<tr>
<td>21</td>
<td>11-I-0008</td>
<td>Phase I/II, Non-randomized, Multicenter, Open-label Study of G1XCGD (Lentiviral Vector Transduced CD34+ Cells) in Patients with X-Linked Chronic Granulomatous Disease</td>
<td>NIAID</td>
<td>2019</td>
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<tr>
<td>22</td>
<td>11-I-0007</td>
<td>Lentiviral Gene Transfer for Treatment of Children Older than 2 Years of Age with X-Linked Severe Combined Immunodeficiency</td>
<td>NIAID</td>
<td>2019</td>
</tr>
<tr>
<td>23</td>
<td>13-C-0016*</td>
<td>A Phase I Study of an Adenoviral Transduced Autologous Dendritic Cell Vaccine Expressing Human HER2/neu ECTM in Adults with Tumors with 1-3+ HER2/neu Expression</td>
<td>NCI</td>
<td>2020</td>
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<tr>
<td>24</td>
<td>N/A</td>
<td>Autologous oxidase subunit mRNA-corrected granulocyte transfusions to treat patients with chronic granulomatous disease with intractable bacterial or fungal infections</td>
<td>NIAID</td>
<td>2020</td>
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<tr>
<td>25</td>
<td>15-C-0075*</td>
<td>A Randomized, Placebo-Controlled Phase II Study of Multi-Epitope TARP Peptide Autologous Dendritic Cell Vaccine Vaccination in Men with Stage D0 Prostate Cancer</td>
<td>NCI</td>
<td>2021</td>
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<td>26</td>
<td>15-C-0076*</td>
<td>A Pilot Study of Long Term TARP Vaccination Using A Multi-Epitope TARP Peptide Autologous Dendritic Cell Vaccine Vaccination in Previously Vaccinated Men on NCI 09-C-0139</td>
<td>NCI</td>
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<td>14-H-0111</td>
<td>Treatment of an individual patient with sickle cell disease with CD34+ selected, nonmyeloablative haploidentical peripheral blood stem cell transplantation</td>
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<td>28</td>
<td>14-C-0059*</td>
<td>A Phase I Trial of T Cells Expressing an anti-GD2 Chimeric Antigen Receptor in Children and Young Adults with GD2+ Solid Tumors</td>
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<td>29</td>
<td>N/A</td>
<td>CCR4-CAR T cells for T cell lymphomas</td>
<td>NHLBI</td>
<td>2021</td>
</tr>
</tbody>
</table>
**Next Steps**

1. Implement new policy
2. Identify next scarce resource for prioritization
   
   *Challenge: some protocols utilize multiple scarce resources adding complexity to the prioritization process*

3. Evaluate metrics to monitor success of policy and in future consider broadening policy to entire IRP clinical research portfolio.
Conclusion

The policy on scientific review with prioritization of scarce resources is expected to improve the quality of science and provide a rational and transparent process to utilize critical scientific elements at the Clinical Center.