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

Clinical Center Research Hospital Board
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Outline

- Scientific Review of Clinical Protocols
- Prioritization of Protocols Using Scarce Resources at the CC

IRP Clinical Protocol Activity*

Total Clinical Protocols in Intramural Program: 2171

	Clinical Center	Off site
	1636	535
Interventional Clinical trials	800	52
Phase 1	268	20
Phase 2	479	18
Phase 3	42	9
Phase 4	11	5
Natural History	740	471
Training	27	1
Screening	69	11

* 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.

Scientific Review IT Requirements

- 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

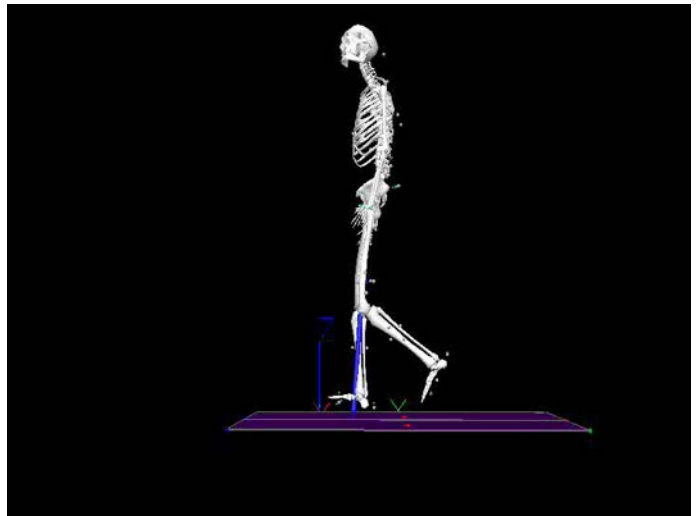
- Cell processing; apheresis services
- Imaging (MRI/MRI PET/CT)
- Research PET-scan slots; availability of new radiotracers
- Bone marrow/stem cell transplantation
- Operating rooms
- Metabolic chambers

Multi-modality minimally invasive procedural suite

Metabolic chamber

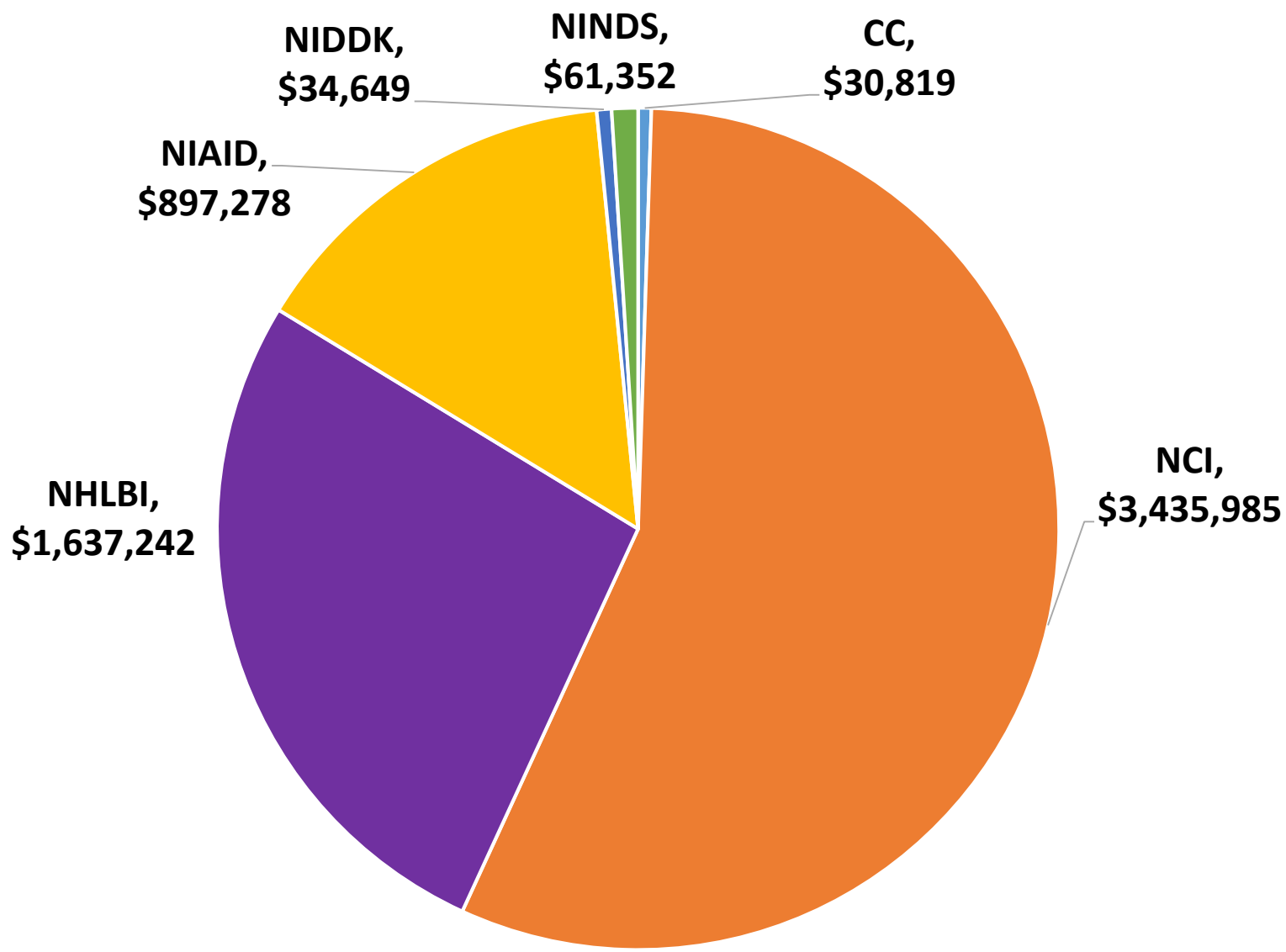
Scarce Resources at the Clinical Center-cont.

- 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



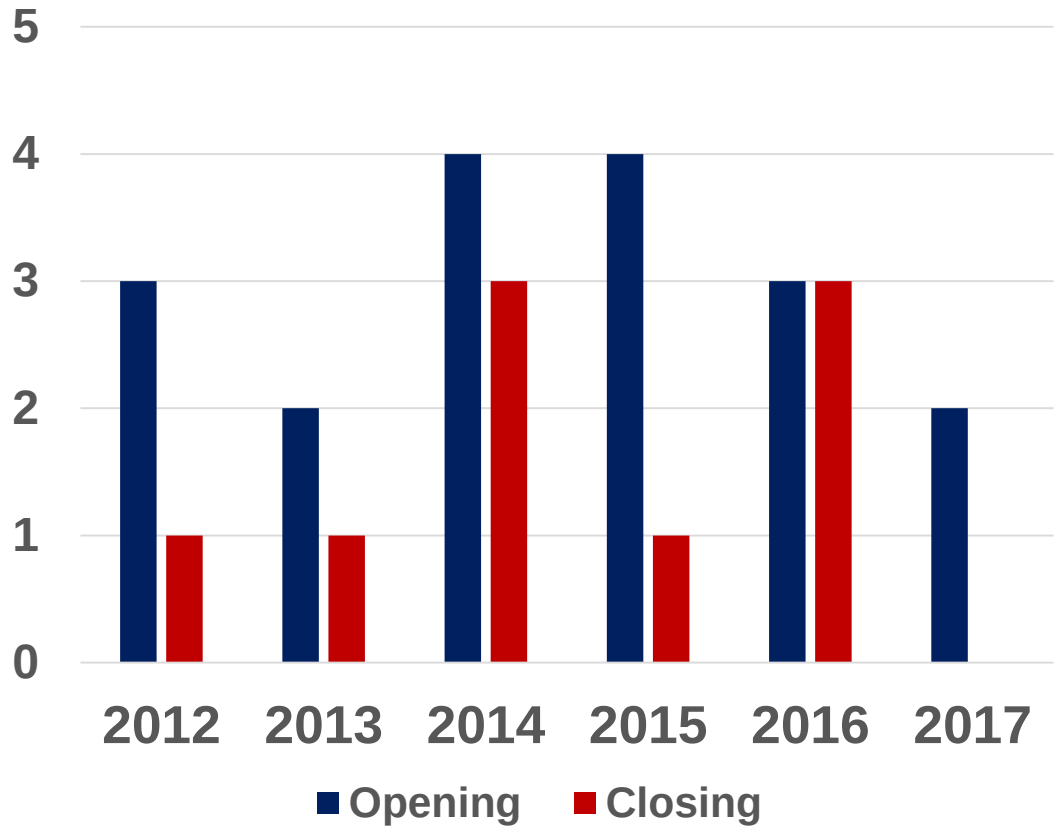
Cell Processing in Department of Transfusion Medicine as Pilot for Prioritization

IC Utilization of Cell Processing Services FY16

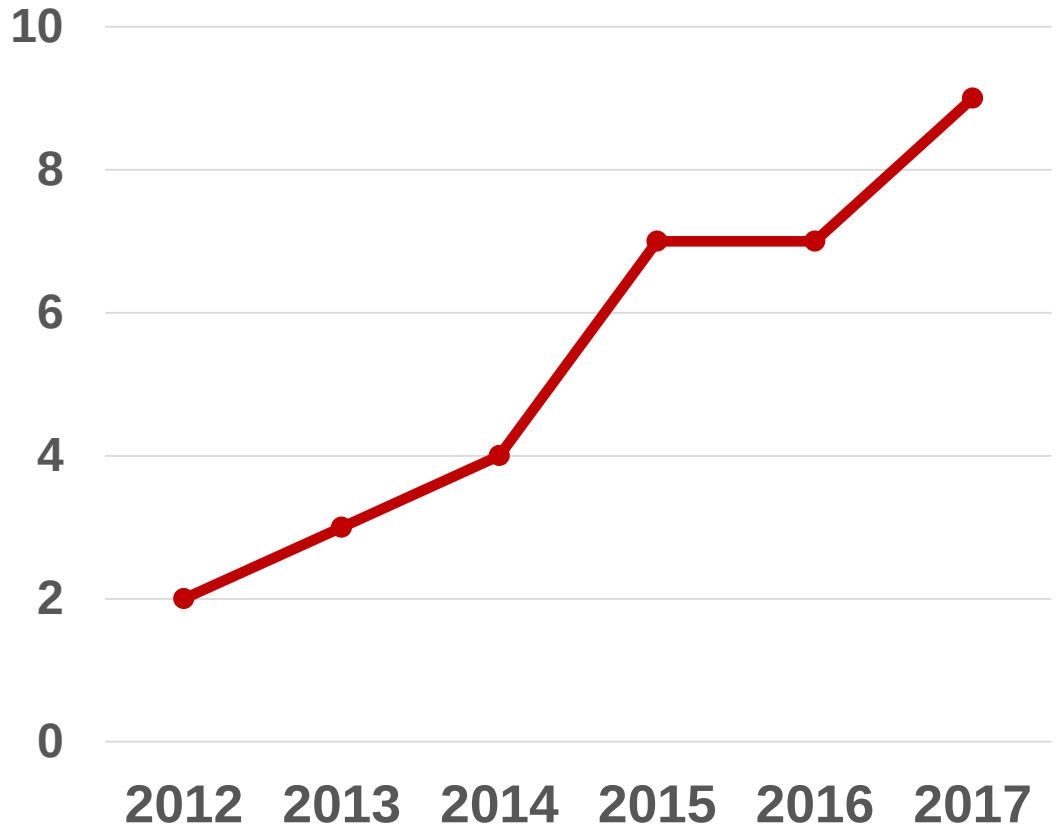


Change in Number of IND Cell Processing Protocols in DTM 2012-2017

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**
  - **5 Complex Hematopoietic Stem Cell (HSC) Transplants**
  - **18 Complex Cell and Gene Therapy**

  (13 complex protocols in queue because lack of tissue culture rooms)
  - **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)**
  - **1 ready 2017**
  - **7 ready 2018**
  - **2 ready 2019**
  - **10 ready 2020**

Cell Processing Activity-continued

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

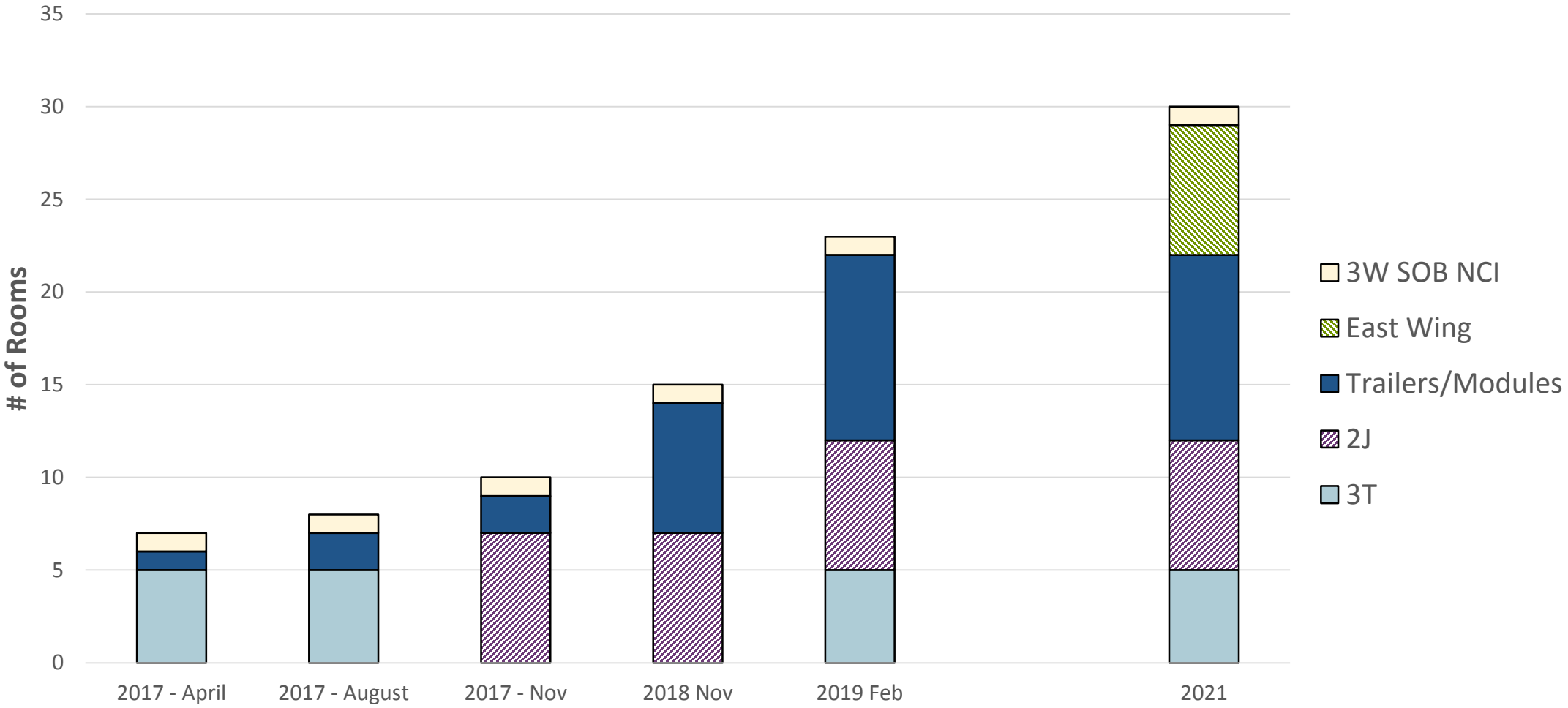
  Note: when 2J opens 3T closes for 6 mo renovation

- 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

Space Availability



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.

Prioritization Process cont.

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

#	Protocol #	Protocol Title	Institute/ Center	Expected Completion Year
1	10-H-0154	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	NHLBI	2019
2	N/A	Autologous Cell Therapy for Age-Related Macular Degeneration Using Patient-Specific Induced Pluripotent Stem (iPS) Cells	NEI	2020
3	N/A	TSLPR-CAR T cells to treat B cell leukemia	NCI	2021
4	10-C-0054*	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)	NCI	2019
5	14-C-0168*	A Phase I Clinical Trial of T Cells Targeting B-Cell Maturation Antigen for Previously Treated Multiple Myeloma	NCI	2018
6	16-C-0054*	T Cells Expressing a fully-human anti- CD19 Chimeric Antigen Receptor for treating B-cell malignancies	NCI	2018
7	16-C-0163*	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	NCI	2018
8	17-C-0048*	T Cells expressing a fully-human anti-CD30 Chimeric Antigen Receptor for treating CD30-expressing lymphomas	NCI	2019
9	N/A	A Randomized Phase I/II Trial of T Cell Receptor Gene Therapy Targeting HPV-16 E6	NCI	2018
10	15-C-0029*	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	NCI	2019
11	N/A	CD19/CD22 Bi-specific CAR T cells	NCI	2021
12	N/A	Gene correction of Leukocyte Adhesion Deficiency (LAD) CD18 CD34+ cells	NHLBI	2020
13	16-N-0072*	A Pilot Study of Adoptive Cellular Immunotherapy for Progressive Multifocal Leukoencephalopathy with *Ex Vivo* Generated Polyomavirus-Specific T-cells PyVST for PML	NINDS	2021
14	11-C-0016	Rapamycin-Resistant T Cell Therapy of Multiple Myeloma: Relapse Prevention and Relapse Therapy,"	NCI	2017
15	17-C-0011*	Phase 1 Study of intraperitoneal 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	NCI	2020
16	08-H-0186*	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 –TRAIL cytotoxicity with Bortezomib	NHLBI	2019
17	14-H-0182*	Phase I/II Trial of Early Infusion of Multivirus Specific T cell (MVST) to Prevent Post Transplant Viral Infections	NHLBI	2017
18	08-H-0046	Co-Infusion of umbilical cord blood and haploidentical CD34+ cells following nonmyeloablative conditioning as treatment for severe aplastic anemia and MDS associated with severe neutropenia refractory to immunosuppressive therapy	NHLBI	2017
19	13-H-0144	Peripheral blood stem cell allotransplantation for hematological malignancies using ex vivo CD34 selection – a platform for adoptive cellular therapies.	NHLBI	2018
20	14-H-0180	Ultra Low dose IL-2 Therapy as GVHD Prophylaxis in Haploidentical Allogeneic Stem Cell Transplantation	NHLBI	2017
21	11-I-0008	Phase I/II, Non-randomized, Multicenter, Open-label Study of G1XCGD (Lentiviral Vector Transduced CD34+ Cells) in Patients with X-Linked Chronic Granulomatous Disease	NIAID	2019
22	11-I-0007	Lentiviral Gene Transfer for Treatment of Children Older than 2 Years of Age with X-Linked Severe Combined Immunodeficiency	NIAID	2019
23	13-C-0016*	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	NCI	2020
24	N/A	Autologous oxidase subunit mRNA-corrected granulocyte transfusions to treat patients with chronic granulomatous disease with intractable bacterial or fungal infections (MaxCyte)	NIAID	
25	15-C-0075*	A Randomized, Placebo-Controlled Phase II Study of Multi-Epitope TARP Peptide Autologous Dendritic Cell Vaccination in Men with Stage D0 Prostate Cancer	NCI	2020
26	15-C-0076*	A Pilot Study of Long Term TARP Vaccination Using A Multi-Epitope TARP Peptide Autologous Dendritic Cell Vaccination in Previously Vaccinated Men on NCI 09-C-0139	NCI	2019
27	14-H-0111	Treatment of an individual patient with sickle cell disease with CD34+ selected, nonmyeloablative haploidentical peripheral blood stem cell transplantation	NHLBI	2017
28	14-C-0059	A Phase I Trial of T Cells Expressing an anti-GD2 Chimeric Antigen Receptor in Children and Young Adults with GD2+ Solid Tumors	NCI	Closed
29	N/A	CCR4-CAR T cells for T cell lymphomas	NCI	2021

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.