**CTTC 2501: A Pragmatic Randomized Trial comparing Antithymocyte Globulin (ATG) or Post Transplant Cyclophosphamide (PTCy) with ATG plus PTCy Prophylaxis against Acute and Chronic Graft Versus Host Disease (aGVHD, cGVHD) in Matched Donor Hematopoietic Cell Transplants (HCT).**

## Background and Rationale

Both **antithymocyte globulin (ATG)** and **post-transplant cyclophosphamide (PTCy)** are widely used as graft-versus-host disease (GVHD) prophylaxis strategies in allogeneic hematopoietic cell transplantation (HCT). Each approach independently reduces the risk of acute and chronic GVHD without significantly compromising relapse rates.

We demonstrated with the CTTC 1901 trial the safety of this combination approach, with no increased toxicity seen, and lower rates of acute GVHD demonstrated. A definitive trial showing improvement in chronic GVHD, relapse free survival would be required to change practice.

This trial addresses this critical knowledge gap using a **pragmatic design** that reflects real-world decision-making and allows for center-specific standards, making it both **feasible and broadly generalizable**.

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## Study Design

- **Design:** Multicenter, pragmatic, open-label randomized controlled trial
- **Randomization unit:** Individual patient
- **Physician-driven stratification:** Each site/physician selects **either ATG or PTCy** as their preferred standard GVHD prophylaxis based on local practice and patient-specific factors
- **Randomization:** Patients are randomized 1:1 to either:
    - **Arm A:** Physician-selected standard prophylaxis (ATG or PTCy), or
    - **Arm B:** Combination of ATG + PTCy

This design respects physician judgment and enhances participation while directly testing the incremental benefit of dual immunosuppression.

**Primary Endpoint**

- **Chronic GVHD-Relapse-Free Survival (CGRFS):** Defined as survival without moderate-to-severe chronic GVHD or relapse of underlying malignancy

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**Eligibility Criteria (Key Elements)**

- Age greater than 16
- Malignant hematologic disease (e.g., AML, ALL, MDS, lymphoma)
- Matched related or unrelated donor (≥7/8 HLA match at A, B, C, DRB1)
- Peripheral blood stem cell graft (HPC-Apheresis)
- Eligible for myeloablative or reduced-intensity conditioning
- Karnofsky performance status ≥60%
- Ability to consent and comply with follow-up

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**Treatment and Monitoring**

- Conditioning and supportive care regimens are per institutional standards
- ATG dose determined by centre – ranges between 2 mg/kg and 4.5 mg/kg will be considered
- PTCy is administered as 50 mg/kg on days +3 and +4 post-transplant
- GVHD, relapse, survival, infectious complications, immunosuppression burden, and patient-reported outcomes are monitored

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**Why Participate?**

- Resolves a key question regarding **synergistic use of ATG and PTCy** in clinical practice
- Known **safety** of the combination based on the pilot trial results
- Designed for **flexibility** and **minimal disruption** to local transplant workflows, by emphasizing
- Generates **practice-changing data** using a highly relevant, real-world model
- Incorporates **biobanking and correlative studies** to explore mechanistic biomarkers
- High-impact primary endpoint (CGRFS) aligned with long-term functional outcomes

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| Title | A Pragmatic Randomized Trial comparing Anti-Thymocyte Globulin (ATG) or Post Transplant Cyclophosphamide (PTCy) with ATG plus PTCy Prophylaxis against Acute and Chronic Graft Versus Host Disease (aGVHD, cGVHD) in Matched Donor Hematopoietic Cell Transplants (HCT). |
| Hypothesis | The combination of ATG and PTCy will result in superior CGRFS compared to current standard of care (ATG or PTCy alone) |
| Design | Multicenter, Non-Blinded, Randomized Pragmatic Trial |
| Sponsor | University of Manitoba |
| Administrative Support | Cell Therapy and Transplantation Canada (CTTC) |
| Funding | TBD |
| Sample size | TBD |
| Primary endpoint | The primary endpoint is chronic graft versus host disease, relapse free survival (CGRFS) |
| Inclusion Criteria | Ages 16-70, transplant being performed for a malignant disease, blood progenitor cell grafts from MHC matched (8/8) family or unrelated donors (8/8 or 7/8), and either myeloablative or reduced intensity conditioning. |
| Exclusion Criteria | Poor condition (centre determined), active infection, HIV infection, T-cell antibody prophylaxis (anti-CD52), use of cord blood grafts or T-cell depleted grafts, bone marrow graft |
| Preparative Regimens | Myeloablative or Reduced Intensity protocol (to be declared at outset) |
| Supportive measures | Institutional practices. Quantitative EBV testing is strongly recommended. |
| Anti-Thymocyte Globulin | Thymoglobulin® 4.5 mg/kg total dose (schedule: 0.5 mg/kg day -2; 2.0 mg/kg days -1 and +1) – all participants. |
| Cyclophosphamide PTCy | Cyclophosphamide 50 mg/kg IV on days +3 and +4, for those randomized. |