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Protocol

The transfusion-associated dyspnea prospective observation and laboratory assessment study: a protocol for investigating and disambiguating cardiopulmonary and high-grade febrile transfusion reactions in adults

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ABSTRACT

Background: Cardiorespiratory transfusion reactions drive most transfusion-related morbidity and mortality. Transfusion-associated circulatory overload and transfusion-related acute lung injury have established causes, important impacts, mitigation options, and revised definitions, while non-conforming CRTRs fall into a category known as transfusion-associated dyspnea. Though procedures to investigate high-risk febrile transfusion reactions are typically rooted in detecting incompatibility or bacterial contamination, a common standard for examining CRTRs is lacking. CRTRs are further challenged by charting limitations, confounding (or enhanced susceptibility) by comorbidities, and/or overlapping insults. Deeper profiling of CRTRs could improve categorizations, reveal best-value diagnostics, and decipher the nature of (and/or minimize) reactions coded as TAD.
Methods: The primary objective of this multi-center study is to reduce uncertainty in final conclusions drawn on CRTRs (cases), defined by dyspnea with objective disturbances and/or significant hemodynamic insults, with/without fever (±F). HRFTRs (controls) represent higher-grade F (T≥39°C or chills/rigors or lower-grade F (≥38°C by +Δ1°C) with non-respiratory effects). Patients (goal: 200) consent to additional sampling (≤24h post-TR) to identify contributing factors in case/control presentations, and in diagnostic groups (TRALI, TACO±F, TAD). Mechanistic axes of interest are cardiorenal, hemolytic, leukoagglutinating, biolipid, vasoactive, and inflammatory. Secondary goals include elucidation of real-life "insult-multiplicity" in CRTRs, tests of greatest yield, and distinguishing features in TRALI/TACO/TAD.
Conclusions: A deep systematic CRTR probe may not only reduce diagnostic uncertainty but frame biomarker performance and pathologic signatures in definition-specific CRTRs. The re-classifiability or biology of TAD may be better understood. High-quality, mechanistic, true-to-quantity hemovigilance better exposes burdens and management options.
Trial Registration: The trial is registered with ClinicalTrials.gov. with registry number NCT04267029.

Keywords: Transfusion, Hemovigilance, TAD, TACO, TRALI, Fever

INTRODUCTION

Cardiorespiratory transfusion reactions as the deadliest and collectively most impactful adverse events in transfusion

While blood transfusions are among the most commonly performed procedures in healthcare, and each encounter entails a certain risk of adverse events, cardiorespiratory transfusion reactions (CRTRs) individually and collectively stand out as the most significant of acute residual harms. CRTRs may reflect pulmonary edema that is either cardiogenic (i.e., hydrostatic transfusion-associated circulatory overload (TACO), occurring in 1-10% of transfusions), or non-cardiogenic (i.e., a permeability event producing transfusion-related acute lung injury (TRALI) (Figure 1).[1-6] CRTRs may also incur the direct upper and lower airway and/or cardiovascular effects of an allergic bronchopulmonary or anaphylaxis response.[7,8] Furthermore, CRTRs may occur downstream of the multi-system effects of a bacterially contaminated or incompatible product or its pyrogenic mediators.[9-11] Taken together, CRTRs account for the majority of transfusion-related fatalities, though their true scope in all-cause morbidity and mortality remains unknown.[12-16]

The challenge of accurate CRTR diagnosis and the inherent complexity of cases

In real-life practice, cases often elude classification because of insufficient charting or non-specific diagnostics, failure to meet strict case criteria, pre-existing conditions (which either predispose to, or mimic, CRTRs), and/or co-occuring reactions.[17-22] Given the disproportionate extent of coding-uncertainty in CRTRs, deep/unbiased clinicolaboratory profiling may identify unsuspected pathophysiologic mediators, and consequently enable re-classification of CRTRs that have either been coded as uncertain, incorrect, or incomplete diagnoses or as members of the pragmatic exclusion category known as transfusion-associated dyspnea (TAD) (Figure 2).[16]

Interestingly, TACO appears to be more than mere circulatory overload, exhibiting inflammation and/or pyrexia in 1/3rd of cases, and a non-leukoreduction association.[4,23-26] Endothelial stretch may advance transudation to exudation and cloud the difference between TACO and TRALI.[27,28] Because neither fever nor inflammation are established criteria for TACO, whether such co-presentations distract or dissuade reviewers from recognizing or fully reporting these events is unknown. To what extent the underlying signatures of febrile TACO also overlap with (or deviate from) classic TACO, and/or resemble dyspneic or non-dyspneic febrile non-hemolytic transfusion reactions (FNHTRs), remains to be determined.

The no-less co-febrile (but rarer) entity of TRALI is usually an immune complex event of passive cognate (HLA or HNA specific) donor leukoagglutinins infused into primed recipients.[29-34] However, seronegative cases exist, "transfused ARDS" counts increase despite mitigation, and reverse TRALI is described.[35-43] TRALI may also have a "too-sick" or "not-sick-enough" under-recognition bias, with consideration dismissed despite heightened vulnerability in the already-critically ill on the one hand, and constraints upon serologic examinations on the other, be this due to less serious or convincing cases, costs, and/or hidden tensions on retaining high-value/-performance donors.

Table 1: Sample size calculation.

CRTR uncertainty rate (%)		
Classification by customary methods (Pre-TADPOL)	**Classification after review of clinicolaboratory research file (Post-TADPOL)**	**Required sample size**
60	45	110
60	40	64
60	30	25
50	30	61
50	25	37
40	25	97
40	20	53

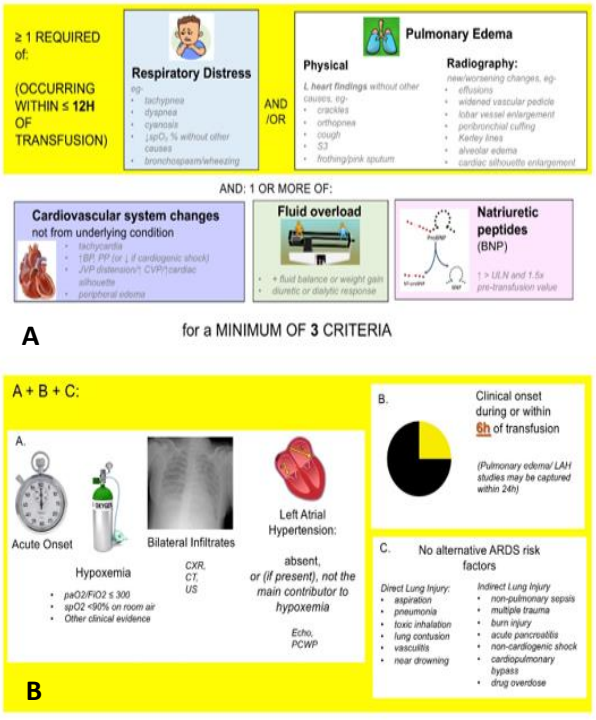

Figure 1: Revised Definitions for (A) TACO and (B) TRALI.[2,6]

Novel mediator testing may characterize new prevention or treatment strategies in TRALI and reveal synergies in classic seropositive cases or independent drivers in

seronegative ones.[44-49] Forced reductionism toward a single diagnosis in hemovigilance potentially dismisses the truth of overlap states or complex presentations. Alternatively, diagnoses may be counted as separate events, despite appearing in a person simultaneously.[50,51] Finally, the occurrence of one problem cannot grant immunity against the other, and independent probabilities exist for adverse events, with the distribution of diagnoses (and vulnerabilities) more often concentrating in a subset of patients.[52,53] Despite these facts, few reports describe the proportion or frequency of adverse transfusion events presenting as two or more simultaneous injuries.[16,23]

The uncertain roots of TAD

TAD is a final diagnosis-of-exclusion in hemovigilance if neither the underlying condition nor a specifically defined harm account for the suspected CRTR. As a basket category guarding against inflated tallies of TRALI or TACO (for those cases falling short in criteria and/or severity), TAD therefore shelters unknown proportions of these and other states, including the possibility of a unique injury group with its own pathogenesis.[10,54] If TAD cases were ideally investigated, what proportion would be re-classifiable? In 37 cases in New Zealand, re-probing deemed 16-22% to be TACO, with 40-43% remaining TAD.[54] While allergic transfusion reactions are among the commonest adverse transfusion events, with mucocutaneous eruptions readily signaling their presence, the absence of integumentary involvement (as in a case of audible wheezing without pulmonary edema) may not suffice to rule out an allergic/bronchospastic transfusion reaction (ABTR).[55] Meanwhile, these ambiguous cases tend not to be subjected to the luxury of assessments for specific immune globulin deficiencies, the emergence of anti-IgA IgG, or rises in IgE, histamine, or tryptase. Cases of isolated post-transfusion hemodynamic shock (lacking allergic stigmata) may in turn be explained by other pathways (such as those impairing bradykinin clearance), but testing for this is also rare.[56] The serious hazards of transfusion–United Kingdom Haemovigilance system 2020 report distinguished between cases defaulting to TAD-due-to- insufficient-information versus TAD-as-confident-diagnoses-of-exclusion at a >3:1 ratio.[57] From the International haemovigilance network database for the surveillance of adverse reactions and events (25 countries, 2006-2012, n=92,850 reactions), TAD accounted for ~2% of reactions, with an incidence therefore sitting between TACO and TRALI.[15] Without further research, the recourse of a non-pathophysiologic "convenience" category in TAD stands to keep undermining our understanding of CRTRs at a qualitative and quantitative level.

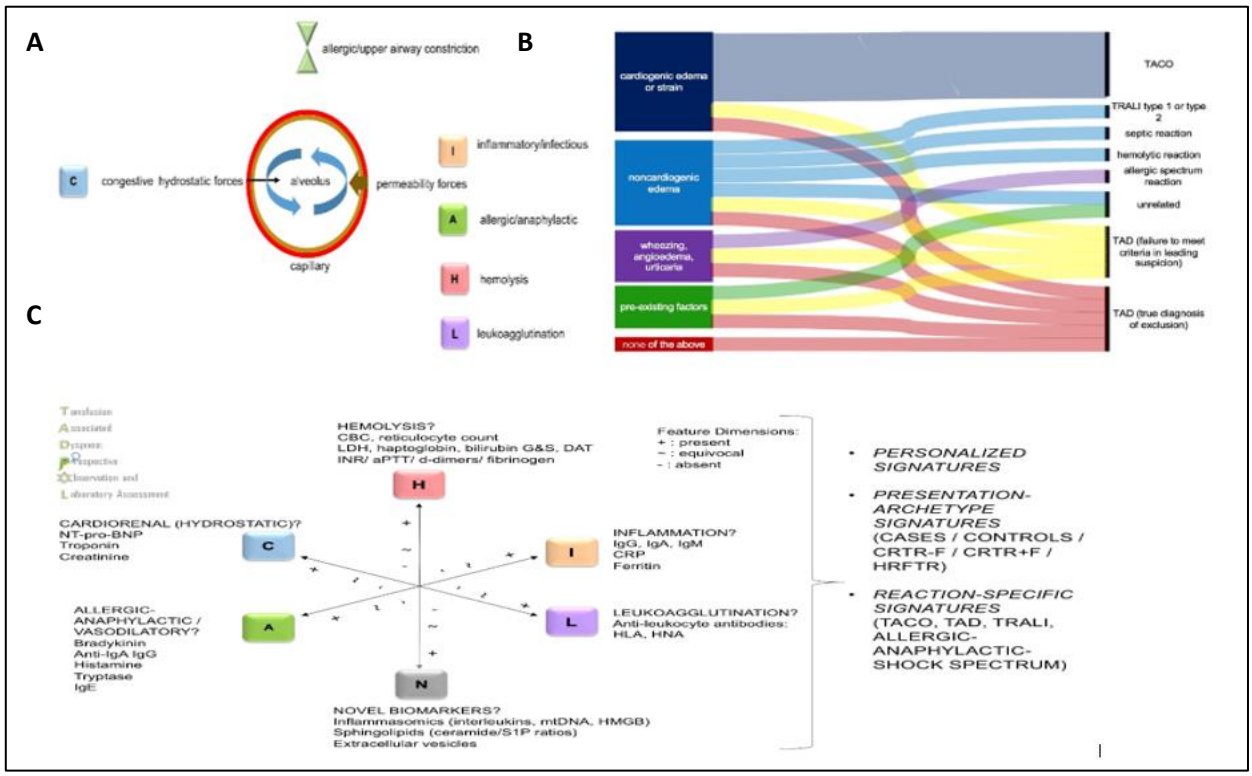

Figure 2: Models of injury in cardiorespiratory transfusion reactions (CRTRs); (A) inter-relating and/or indistinguishable forces upon an alveolus, (B) CRTR features and possible final diagnoses, (C) multidimensional deconstruction in the TADPOL study.

Aim and objectives

The transfusion-associated dyspnea: prospective observation and laboratory assessment (TADPOL) Study is a means to more deeply characterize CRTRs, with discrete goals in: reducing CRTR coding uncertainties, quantifying factor interactivity/("complexity") inherent to CRTRs, and observing clinicolaboratory signatures for TAD and other defined reactions (Figure 2). In quaternary aims, TADPOL also establishes a hypothesis-generating database and bioarchive, linking donor/product and patient/event information, for the benefit of machine learning and other advanced analyses.

METHODS

Study population and sampling methods

This is a prospective (observational) nested case-control study in transfused patients with transfusion reactions, seeking to enrol 200 patients by written informed consent. Enrolled presentation archetypes are to divide evenly between cases (CRTRs) and controls (selected from the greater abundance of high risk febrile transfusion reaction (HRFTR) patients) (Figure 3). This multi-centre study is conducted at 6 large academic adult-care hospital facilities across 4 institutions affiliated with the University of Toronto: the University Health Network (UHN: [3 sites: Toronto General Hospital (TGH), Princess Margaret Hospital (PMH), Toronto Western Hospital (TWH)]); Sunnybrook Health Sciences (SBK); Mount Sinai Hospital/Sinai Health (MSH); and St. Michael's Hospital/Unity Health Toronto (SMH). In this urban/academic hospital network, >100,000 blood components were given in 2017, accounting for roughly 10% of Canada's blood product administrations. At the UHN, 3-5% of blood product recipients suffer transfusion reactions, suggesting a steadfast reporting rate.[58,59] Inpatients and outpatients across various healthcare settings are included, and each enrolled patient undergoes protocol-defined multi-dimensional biomarker sampling within 24 hours of the TR onset in accordance with timing-related resources, while all enrolees undergo systematic chart abstractions for data fields pre-specified in the case report form. Eligible CRTRs are those occurring within 12 hours of a transfusion, and are defined as having either of the following: hypoxic desaturation, and/or cardio/pulmonary distress, as characterized by at least 2 of: subjective difficulty breathing or chest pain, and/or objective signs including: (any one or more of): tachypnea, increased work of breathing, new or worsened adventitious breath sounds, new or worsened tracheal fluid outputs, cardiovascular changes of significance (tachycardia, hyper- or hypo-tension, jugular or central venous pressure rises, or cutaneous signs of shock/hypoperfusion).[60] HRFTRs are the comparator (non-CRTR) arm with patients who have met criteria for fevers of significance: temperatures at or exceeding 39°C by a rise of at least 1°C, and/or chills/rigors, and/or lesser thermal rises but with features suspicious for higher-risk events (non-cardiopulmonary pain, cardiovascular changes not meeting CRTR criteria, panic, etc). The hospital transfusion laboratory at each site centrally receives reports of suspected transfusion-associated harms, each of which are screened in real-time by a transfusion safety officer and on-call transfusion medicine physician (NS, KP, AG, YL, LL, JP, JC, CC), thereby permitting assessment for eligibility and appropriate count-stratification and management (Figure 4). There are no exclusions based on sex, race/ethnicity/geo-ancestry. However, grounds for recusal include pregnancy, massive hemorrhage (>20 implicated products in the 24 hour period before the TR), prior enrolment in the same arm of the study, anticipated discharges (including foreseeable death) before the ability to complete essential on-site tasks of the 24 hour post-TR window, a patient not granting consent (either declining in real-time or withdrawing at any time subsequently), the most responsible physician advising against enrolment for any reason, or the maximum anticipated investigative blood volume being deemed too high in relation to patient habitus (sample volume sums typically <70 ml).

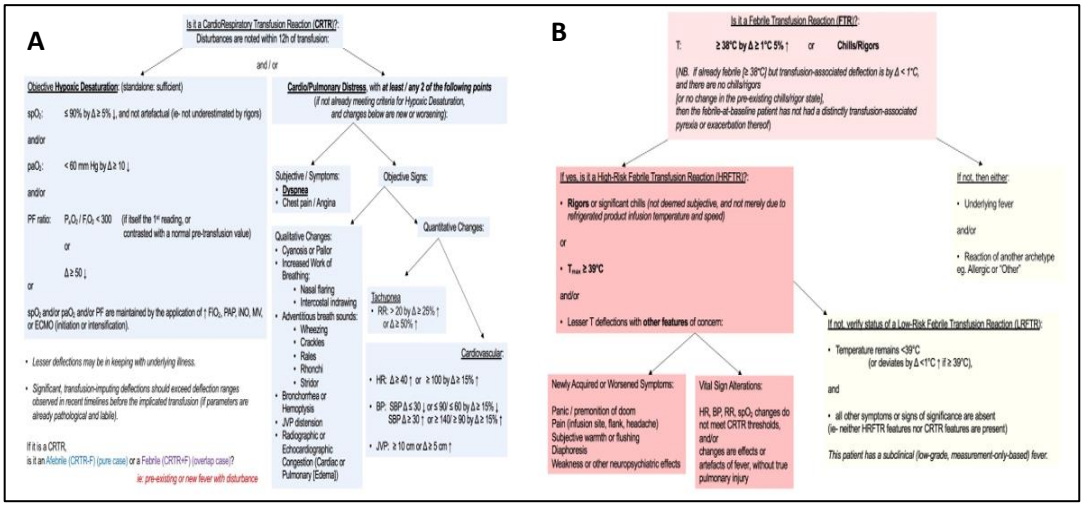

Figure 3: (A) Cases (CRTRs), (B) controls (HRFTRs).

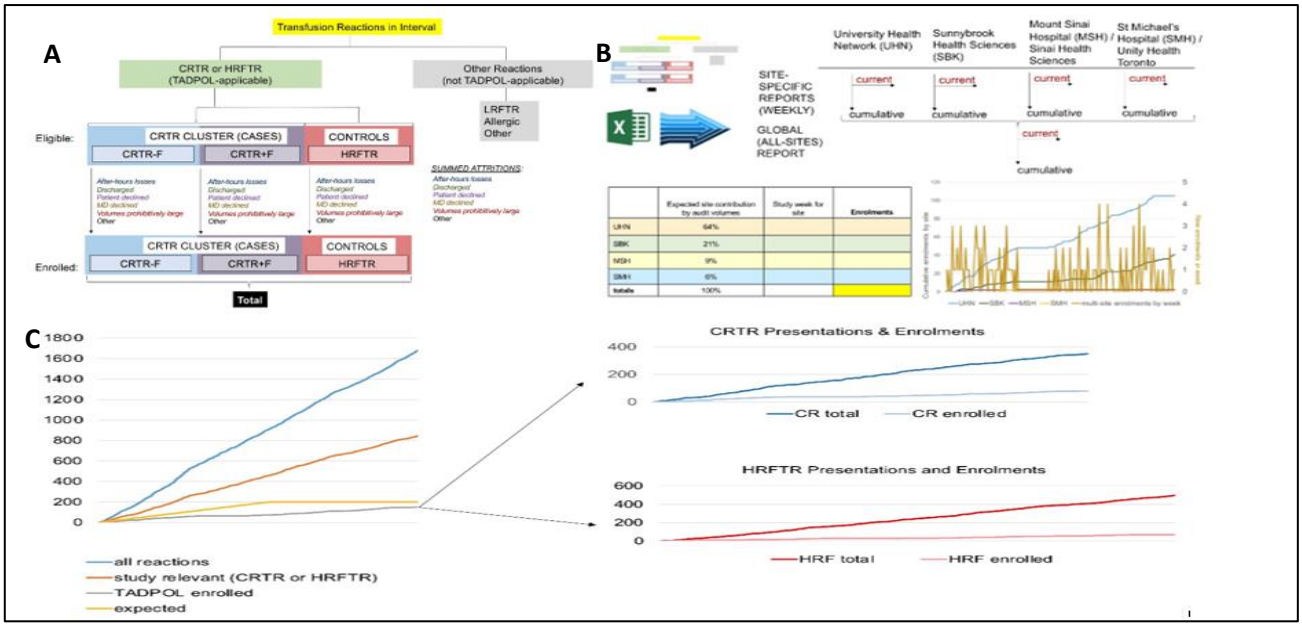

Figure 4: Cases (CRTRs) and controls (HRFTRs): (A) transfusion reactions: presenting archetypes and classification flow in TADPOL, (B) site contributions in TADPOL, (C) archetype flow over time.

Processes and statistical analysis

Eligible patients are approached by study personnel clinical research coordinators (CRCs: SS, RS, CA, AK) after authorization by the patient's most responsible physician. Patients interested in participating are provided with a study pamphlet and a written informed consent form. Capable participants have the opportunity to ask questions and consult with their care team. If a patient is unable to consent, then the substitute decision maker is selected. All sites maintain annual research ethics board (REB) approval of the study's operations. There are no costs to patients or compensation. By study participation, greater compliance with the minimum, policy-prescribed standard of case-investigative care (and more detailed hemovigilance reporting capability) is anticipated. Data are generated within existing hospital platforms as well as external to the chart, in real-time and post-hoc (at batched analysis and digital upload/integration periods) pursuant to local versus reference laboratory activities respectively. All patient study data are anonymized with a unique patient number (UPN), and aggregated in a multi-authentication password-protected browser EDC base (REDCap®, v11.0.3) with rigorous healthcare institute cybersecurity standards (server: Toronto General Hospital). Site-based patient identifier-to-UPN keys are stored locally under double-locked conditions with access limited to involved local investigators, the CRCs, and PIs (JC, CC). Study patient enrolments and material analyses will take place over a duration not greater than 4 years (1 January 2019 to 31 December 2022). The proposed sample size of 200 was selected pragmatically and by statistical review. In audits since 2017, the study locations collectively process ~500 TRs annually, half of which constitute TADPOL-eligible presentation archetypes (CRTR or HRFTR), with <20% of these predicted to enroll.[61] Whereas uncertainty (i.e., confidence in the provisional diagnosis deemed not better than "possible" (or simply "unable to rule out") runs at roughly 10%, a distinct rate (of 63%) in CRTR was the primary concern and justification for a targeted and deeper-testing approach.[16] The aspirational hypothesis was to reduce CRTR baseline uncertainty ranges from 40-60% to 20-45%. At α 0.05 and β 0.90, by paired Chi-square/McNemar's test for CRTRs prior to and after systematic TADPOL-specified data enrichment, the sample size requirement was 53 to 110 (Table 1). All enrolments undergo the customary site-specific practices in consultation and formal documentation of the final diagnosis/diagnoses. Weekly tabulations of all archetypes, enrollees, and exclusions at every site occurs through the enrolment duration period. The case report form (CRF, v10, 1-Jun-2021) is a detailed, 18-page instrument divided into 11 major sections for: demographics, morphometrics, comorbidities, cardiologic parameters, bronchopulmonary parameters, current admission details, transfusion/ immunohematology history, TR details, blood services provider data: product/donor information, HLA & HNA antibody investigations, novel biomarker assays (biolipidomics: sphingolipids and extracellular vesicle concentrations), and future assays, pending further funding (i.e., inflammasomics and damage associated molecular patterns (DAMPS) such as HMGB and mtDNA with cytokine profiling). TGH at UHN is the final biorepository for all frozen and batched patient and product specimens from all sites. Cryovials are stored and shipped at a minimum temperature of -20°C until batched testing according to the planned site and time of analysis (Figure 5).

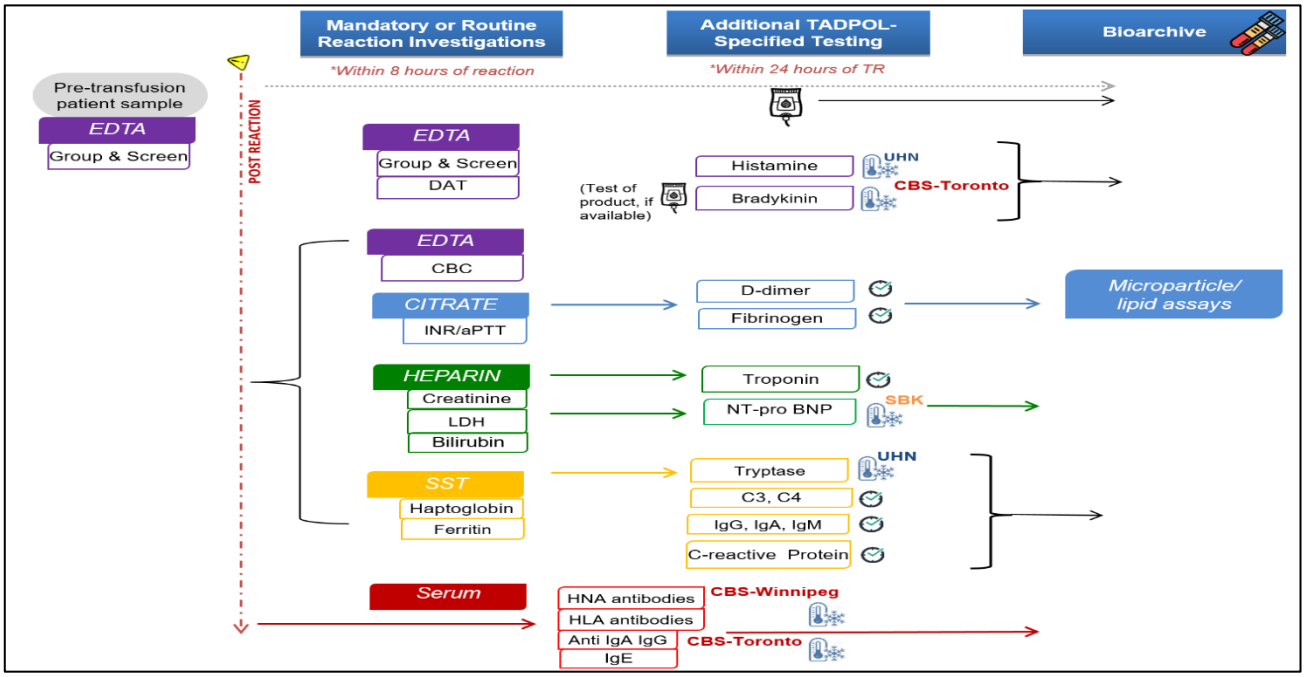

Figure 5: TADPOL specimen sampling and management.

Quality controls for data integrity run throughout the study with cooperative CRC checks of hard-copy and digital CRF fields for completeness, consistency, and logic/validity. Data monitoring occurs quarterly (N=50, 100, 150, 200) to assess for protocol adherence, futility, and ongoing financial feasibility if the enrolment sum remains <200 while the study is within the boundaries of the grant support period (up to 31 December 2022). At the conclusion of the TADPOL study enrolment period (planned for 3 October 2022), and after complete data integration in each UPN REDCap account, paired reviewers (external to/unique from the original site reviewers) re-assess assigned cases and controls, and either verify the original conclusions and associated degrees of certainty, or provide a revised consensus on alternative or additional diagnoses (and the confidence of each therein) (Figure 6). Of analytic interest are the TADPOL-protocol-associated shifts in diagnostic uncertainty and the specific conclusions reached for the sum of participants, in each of the study arms (cases vs controls), in presentation archetypes (CRTR-F, CRTR+F, HRFTR), and in specific diagnoses of interest (e.g., TRALI, TACO, TAD, FNHTR). Demographics across these groups, outcomes (severity), and biomarker performance/distributions will likewise be assessed. Measures of complexity in TRs will include the ranges of presenting abnormalities, (ordinal/categorical) multi-axis injury signatures, and the number of considered diagnoses in the pre-specified arms and subgroups after deep post-study adjudication. Injury signatures in TACO with and without fever, and the operating characteristics of key biomarkers in archetypes- or diagnoses-of-interest (such as leukoagglutinin screens or C-reactive protein levels in CRTRs vs HRFTRs) will be scrutinized for predictive-value thresholds. With associated product, mode-of-production, and key donor details (age, sex, medications, donation history, and historic reaction flags), TADPOL UPN account data can undergo logistic regression classification analysis and semi-supervised machine learning approaches for networked variable associations of potential significance. Study results will be made available online through clinicaltrials.gov, published in peer-reviewed journals, and shared through abstracts at local, national, and international scientific/medical meetings and conferences. Presentations and manuscripts will be reviewed by the authors of the current protocol prior to submission. Participants can inquire about study results but will only be granted access to aggregate data.

DISCUSSION

Strengths and potential implications

Transfusion reactions are still classified with difficulty, undercounted, and poorly understood. This prospective, nested case-control study implements a systematic, multi-spoke approach to the presenting archetypes of greatest clinical concern, and it links the conventional and novel data inputs with donor/product information as well.

We hypothesize that this comprehensive and unique exploratory battery will improve diagnostic confidence and accuracy, and frame several neglected matters for the first time from determining the extent of event-complexity (or insult-overlaps) across reaction types to mapping multiparameter biomarker signatures in specific diagnoses, with special attention to the not-uncommon and cryptic state of TAD. By mechanistically dissecting each enrolled event and overlaying the signatures of

specific reaction types, personalized quantum footprints and useful signal-to-noise windows might be fashioned respectively. The latter in turn may offer more objective, quantitative criteria for next-iteration definition revisions. Six key domains (hemolytic, cardiorenal, allergic/ vasodilatory, immuno-inflammatory, leukoagglutinative, and biolipid) use a mix of widely available tests and experimental assays. This strategy was selected to cross-validate and identify sooner- versus- later-scalable options for biomarkers showing scenario-specific value. In stark contrast with febrile transfusion reactions, CRTRs continue to lack a common or standard recommended laboratory approach. Previously restricted and centrally-operated diagnostics (such as those detecting anti-leukocyte alloantibodies) may also prove to be more or less useful than previously thought after this case-control prospective application. With heightened contemporary interest in the impacts of mode of component production or donor-recipient relationships (such as age- or sex-[mis]matching),[63] this study may also provide a small-but-deep interrogation option as an alternative to the large-but-shallow (and conflicting) population files processed thus far. Putative inputs may carry different weights in specific reaction or recipient categories. Finally, machine learning in this dataset may generate new hypotheses or useful sorting algorithms for hemovigilance practice.[64]

Limitations

CRTRs remain infrequently captured events, and thus robust sample sizes are notoriously difficult to achieve in prospective cohorts. Even in a nested case control study, it is possible that signals of interest in cases are found to be no different from the selected controls, as the latter have also suffered an adverse event that justifies testing. Non-reactors would arguably be the best controls, though the odds of their participation in an uncompensated, multi-tube-blood-sampling study have been assumed to be too low to risk trying. Because this study requires written informed consent (without exception waivers), a selection (or exclusion) bias may be introduced, ie- those cases where consent may not be attained may in fact be the most severe and biologically informative ones. It is also possible that parallel research activities (in the CRF and in laboratory testing) will naturally increase the background investigative activity (or clinician attention) in reaction patient care, so that historic gaps in charting details, and the associated challenges in reaching conclusions, are much ameliorated before or by the time the TADPOL-specified assessments are revealed. In other words, there may be "contamination" (improvement) in practice, so that the differences between initial and final conclusions are less striking in the study era. There will inevitably be some site-to-site variability in reporting, though this research collaboration has been proficient, harmonized, and committed in its study experiences, from launch-training to the design and implementation of policies and procedures. The COVID-19 Pandemic has also exerted a challenge and necessitated extensions in the study (from its original 2-year 2019-2020 plan) to a near-doubling of the total recruitment period.

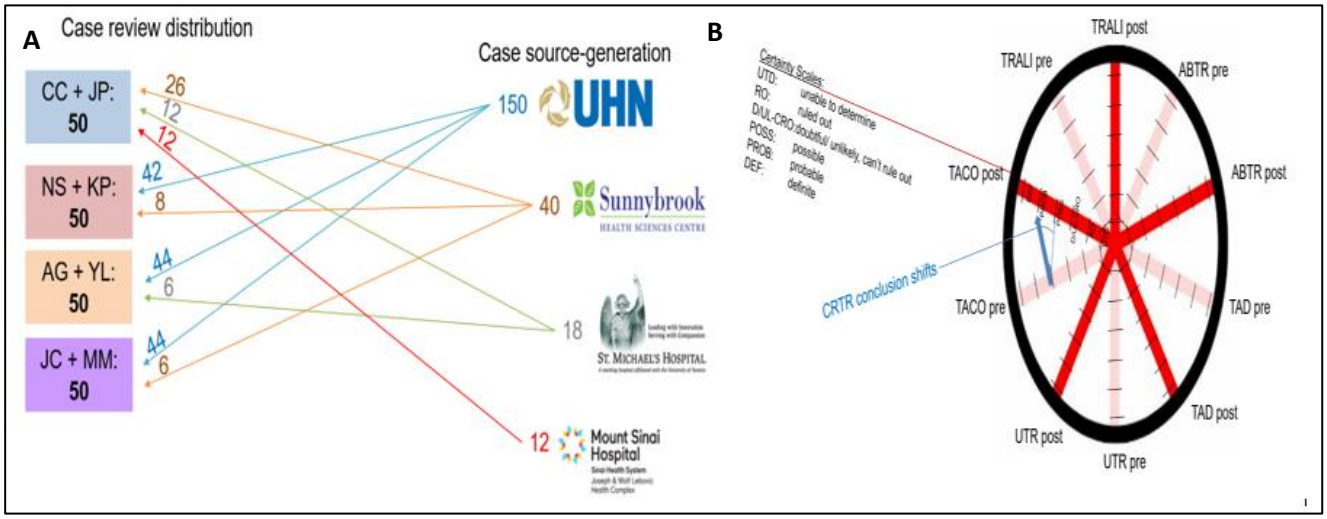

Figure 6: TADPOL study diagnostic adjudications, A) sample external dual reviewer assignments for final diagnosis validation or revision, B) confidence/certainty scale shifts in diagnostic categories with TADPOL detailing.

CONCLUSION

The "Hawthorne effect" refers to changes that the act of observation have on a phenomenon being studied, and it applies especially well in hemovigilance, where we try to respond handily to perceived threats with counter-responses in donor and patient management. However, TRALI persists; the burden of TACO is virtually

unrivalled (in absolute numbers and injury severities); and many CRTRs continue to be coded as TAD (providing no insight). Detailing CRTRs (rather than assessing broadly for incidence with problematic or poorly validated definitions) is the proposed strategy for advancing our understanding. Failed reaction classifications will mislead us in our estimations of risk, bias our perceptions, and frustrate our risk-reduction strategies. The TADPOL approach may improve diagnostic confidence, appraise the complexity of CRTRs and HRFTRs, and inform future objective diagnostic criteria in controversial, evolving, or weak definitions, with TAD being the ultimate case or invitation in point.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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