Intervention Prioritisation Plan for the TIGERS Platform Trial – DRAFT

Proposing an Intervention for Consideration for Evaluation in the TIGERS Platform

We welcome proposals from academic and industry partners for potential interventions to be evaluated in the TIGERS platform. Proposals may be for re-purposed drugs or assets suitable for phase II study in our target population.

To assist with the process, we will ask those wishing to propose an intervention to complete a standardised summary for the drug, based on the questions below. This will request information on the evidence for efficacy, safety, and pharmacology, along with data required to judge the feasibility of including the intervention in the platform.

Complete proposals will first be considered by the TIGERS intervention selection committee. Interventions will be assessed against pre-defined criteria as defined below. Based on these criteria and the available evidence, this committee will then make recommendations to an independent intervention committee. The independent committee will advise the trial management group, who will make the final decision about inclusion into the platform.

The Trial Steering Committee and Data Monitoring Committee will be informed of the plan to introduce a new intervention prior to the commencement of the intervention.

It is anticipated that new interventions will join the platform at intervals, as others graduate or end. Over time, the evidence supporting interventions is likely to evolve. Therefore, interventions deemed to have insufficient support at the time of assessment will continue to be periodically reconsidered.

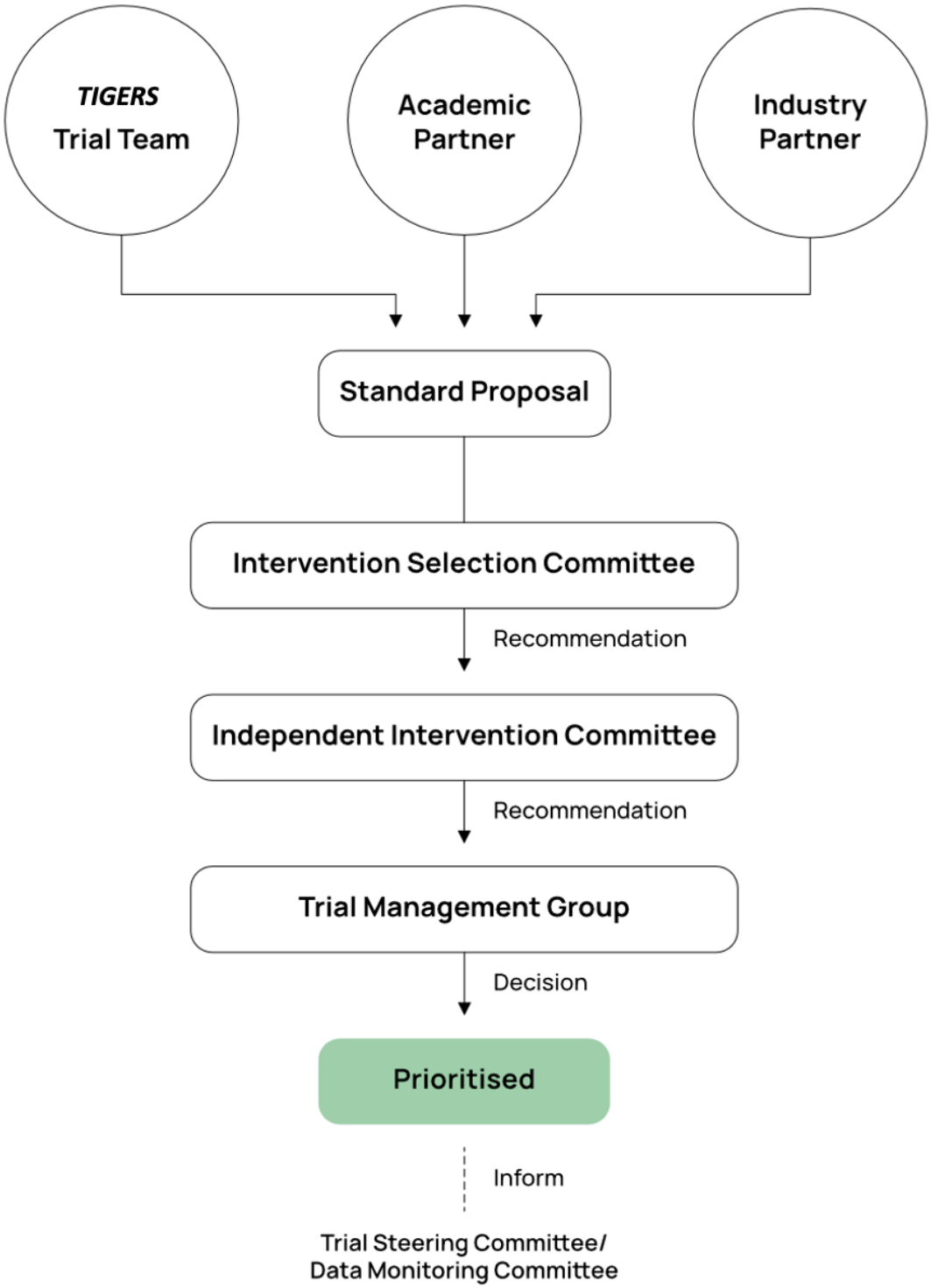

Figure 1: Proposed pathway for interventions entering the TIGERS platform

Initial TIGERS intervention selection committee membership

(arrangements for rotation of chair/membership TBD)

Chair

Prof Manu Shankar-Hari (King's College London, United Kingdom)

Members

Prof Julian Knight (Oxford University, United Kingdom)

Dr Emma Davenport (Sanger Institute, United Kingdom)

Prof Anthony Gordon (Imperial College London, United Kingdom)

Prof Danny McAuley (Queen's University Belfast, United Kingdom)

Prof Alistair Nichol (Monash University, Australia)

Dr Dhruv Parekh (University of Birmingham, United Kingdom)

Dr David Antcliffe (Imperial College London, United Kingdom)

Dr Aidan Burrell (Monash University, Australia)

Prof Bala Venkatesh (The George Institute, Australia)

Prof Naomi Hammond (The George Institute, Australia)

Prof Simon Finfer (The George Institute, Australia)

Dr Sarah Sasson (The Kirby Institute, Australia)

Dr Lachlan Donaldson (The George Institute, Australia)

Prof Antje Blumenthal (University of Queensland)

Others TBD – to include early career researchers appointed to the training posts within TIGERS

Independent intervention committee membership

Chair

Sir Munir Pirmohamed (University of Liverpool, United Kingdom)

Members

TBD – to include clinicians, patient and community representatives, and researchers

Assessment criteria

Candidate interventions will be discussed and assessed by the platform intervention selection committee based on the criteria set out below.

Domain 1 - Evidence base

1.1 Sepsis

- **Is there evidence of efficacy in sepsis?**

Levels:

- Pre-clinical
- Observational
- Randomised controlled trial

Grades: *Strong, moderate, or weak*

1.2 Sub-phenotype

- **Is there evidence of a differential response to the proposed intervention among sub-phenotypes of sepsis?**

Levels:

- Pre-clinical
- Observational
- Re-analysis of a randomised controlled trial

Grades: *Strong, moderate, or weak*

- **Are these sub-phenotypes consistent with the TIGERS platforms approach to stratification?**
- **Is there sufficient evidence to suggest the mechanism by which the intervention exerts benefit and is further investigation of this mechanism tractable within the platform?**

1.3 Other critical illness

- **Is there evidence of efficacy in other inflammatory critical illnesses, for example COVID-19?**

Levels:

- Pre-clinical
- Observational
- Randomised controlled trial

Grades: *Strong, moderate, or weak*

- **Does sufficient mechanistic data exist to show that similar effects could reasonably be expected in a sepsis sub-phenotype?**

Domain 2 - Safety and pharmacology data

2.1 Safety

- **At what phase of development is the intervention?**
- **Does the intervention have important cautions or contraindications?**
- **Does the intervention have important interactions?**
- **What are the common or important side-effects?**
- **Is a reversal agent available?**

2.2 PK/PD data

- **Is robust PK/PD data available?**
- **If so, are data applicable to a critically ill population? Do these data extend to patients in receipt of extra-corporeal therapies e.g. renal replacement therapy?**

Domain 3 - Feasibility

3.1 Suitable formulation

- **Is there a formulation of the intervention that is suitable for administration to critically ill and mechanically ventilated patients?**
- **Does the proposed intervention require special preparation, storage or handling?**
- **What is the anticipated duration of the intervention and what is the dosing schedule?**

3.2 Scalable to trial

- **Is the supply of the intervention scalable to an international, multi-centre study?**
- **Can the supply of the intervention be guaranteed for the anticipated duration of recruitment?**
- **For repurposed interventions, what is the prevalence of use in the population that the trial seeks to include?**
- **Does the intervention require therapeutic drug monitoring?**
- **Does the intervention require the use of an additional biomarker to guide administration?**

3.3 Ongoing or planned studies

- **Are there ongoing or planned studies of the intervention in the same or a similar population? If so, would inclusion of the intervention in TIGERS be likely to offer novel or superior information?**

Current interventions

- Tocilizumab, administered as a single intravenous dose of 8mg/kg (max 800mg) in addition to usual care
- Infliximab, administered as a single intravenous dose of 5mg/kg in addition to usual care

Potential Future Interventions

This list demonstrates the range of therapies that would be suitable for evaluation for inclusion in the TIGERS platform.

Drug Class (Example)	**Evidence for effect in sepsis**	**Potential for heterogeneity of treatment effect (HTE)**
Corticosteroids (hydrocortisone)	Conflicting phase III evidence for mortality benefit (1–3)	Retrospective analysis suggests SRS2 may be harmed (4)
JAK inhibition (baricitinib)	Evidence of benefit in COVID (5, 6)	May inhibit the JAK-STAT mediated emergency granulopoiesis seen in SRS1 (7)
Il-7 (recombinant IL-7)	Increases CD4 lymphocyte proliferation in a cellular model of sepsis (8) Improved organ support free days alive compared to placebo (9) and increased IFNγ producing T-cells (10)	May reverse the T-cell exhaustion associated with SRS1 (7, 11)
Thymosin alpha 1 (thymalfasin)	Possible benefit in sepsis (12). Meta-analysis suggestive of benefit in sepsis (13).	May promotes T-cell differentiation and maturation and improve SRS1 T-cell exhaustion (7, 11)
PD-1 receptor inhibition (Nivolumab)	Safety in small sepsis studies with improvement in cell counts (14, 15)	Could reverse lymphocyte apoptosis induced by septic neutrophils as seen in SRS1 (7)

IL-1 receptor antagonist (anakinra)	Possible benefit in sepsis with evidence of macrophage activation syndrome (high ferritin) (16)	May be more beneficial in those with hepatobiliary dysfunction and disseminated intravascular coagulation (17)
G-CSF (filgrastim)	No statistical benefit to 28-day mortality but direction of effect is in favour of G-CSF in metanalysis of small studies (18)	G-CSF is higher in SRS1 than 2 (7) suggesting that it may worsen the granulopoiesis in this group masking benefit in SRS2
GM-CSF (Sargramostim)	Improves neutrophil function in patients with sepsis (19). Small scale studies in sepsis suggest a signal to benefit. Currently being tested in the SepTiC trial.	May enhance release of immature neutrophils (likely pathological process behind SRS1 (7) so may make SRS1 worse masking benefit in SRS2
Activated protein C (Xigris)	Sepsis is associated with reduced circulating levels of protein C, with plasma levels showing negative correlation with severity of disease and outcomes (20–22). Trials have shown beneficial (23) and null effect (24).	Evidence of effect in a hyper-inflammatory phenotype (25) which has similarities to SRS1 (26). Presence of HTE could account of differences in effect in previous studies.
Immunoglobulins	Metanalysis suggests that intravenous immunoglobulins may reduce mortality in sepsis (27), especially if enriched for IgM/IgA.	Inconsistency of results may be accounted for by HTE. Some evidence of HTE based on patient IgM levels (28)
Mesenchymal stem cell (MSCs)	Diverse properties of MSCs make them a potential therapy for sepsis (29). Small studies suggest potential survival benefits (30)	Diffuse effects make HTE a possibility and can affect cellular function known to be different between SRS groups.
Anti-CTLA-4 (Ipilimumab)	Suggestion of benefit in animal sepsis models (31, 32)	CTLA-4 can downregulate T-cell function so inhibition may improve SRS1 T-cell dysfunction. Treatment with anti-CTLA4 antibody attenuates T cell apoptosis and improves survival in CLP induced sepsis. Specific SNPs in CTLA-4 could serve as prognostic predictors in septic patients (33).

References

1. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, *et al.* Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *New England Journal of Medicine* 2018;NEJMoa1705835.doi:10.1056/NEJMoa1705835.

2. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y, *et al.* Corticosteroids for treating sepsis in children and adults. *Cochrane Database of Systematic Reviews* 2019;2019:.

3. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot J-P, Siami S, *et al.* Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *New England Journal of Medicine* 2018;378:809–818.

4. Antcliffe DB, Burnham KL, Al-Beidh F, Santhakumaran S, Brett SJ, Hinds CJ, *et al.* Transcriptomic signatures in sepsis and a differential response to steroids from the VANISH randomized trial. *Am J Respir Crit Care Med* 2019;199:980–986.

5. Abani O, Abbas A, Abbas F, Abbas J, Abbas K, Abbas M, *et al.* Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *The Lancet* 2022;400:359–368.

6. Ely EW, Ramanan A V., Kartman CE, de Bono S, Liao R, Piruzeli MLB, *et al.* Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. *Lancet Respir Med* 2022;10:327.

7. Kwok AJ, Allcock A, Ferreira RC, Cano-Gamez E, Smee M, Burnham KL, *et al.* Neutrophils and emergency granulopoiesis drive immune suppression and an extreme response endotype during sepsis. *Nature Immunology 2023 24:5* 2023;24:767–779.

8. Venet F, Foray A-P, Villars-Méchin A, Malcus C, Poitevin-Later F, Lepape A, *et al.* IL-7 Restores Lymphocyte Functions in Septic Patients. *The Journal of Immunology* 2012;189:5073–5081.

9. Daix T, Mathonnet A, Brakenridge S, Dequin PF, Mira JP, Berbille F, *et al.* Intravenously administered interleukin-7 to reverse lymphopenia in patients with septic shock: a double-blind, randomized, placebo-controlled trial. *Ann Intensive Care* 2023;13:17.

10. Thampy LK, Remy KE, Walton AH, Hong Z, Liu K, Liu R, *et al.* Restoration of T Cell function in multi-drug resistant bacterial sepsis after interleukin-7, anti-PD-L1, and OX-40 administration. *PLoS One* 2018;13:e0199497.

11. Davenport EE, Burnham KL, Radhakrishnan J, Humburg P, Hutton P, Mills TC, *et al.* Genomic landscape of the individual host response and outcomes in sepsis: A prospective cohort study. *Lancet Respir Med* 2016;4:259–271.

12. Wu J, Zhou L, Liu J, Ma G, Kou Q, He Z, *et al.* The efficacy of thymosin alpha 1 for severe sepsis (ETASS): a multicenter, single-blind, randomized and controlled trial. *Crit Care* 2013;17:.

13. Liu F, Wang HM, Wang T, Zhang YM, Zhu X. The efficacy of thymosin α1 as immunomodulatory treatment for sepsis: a systematic review of randomized controlled trials. *BMC Infect Dis* 2016;16:.

14. Hotchkiss RS, Colston E, Yende S, Crouser ED, Martin GS, Albertson T, *et al.* Immune checkpoint inhibition in sepsis: a Phase 1b randomized study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of nivolumab. *Intensive Care Med* 2019;45:1360–1371.

15. Watanabe E, Nishida O, Kakihana Y, Odani M, Okamura T, Harada T, *et al.* Pharmacokinetics, Pharmacodynamics, and Safety of Nivolumab in Patients With Sepsis-Induced Immunosuppression: A Multicenter, Open-Label Phase 1/2 Study. *Shock* 2020;53:686–694.

16. Leventogiannis K, Kyriazopoulou E, Antonakos N, Kotsaki A, Tsangaris I, Markopoulou D, *et al.* Toward personalized immunotherapy in sepsis: The PROVIDE randomized clinical trial. *Cell Rep Med* 2022;3:100817.

17. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, *et al.* Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. *Crit Care Med* 2016;44:275–281.

18. Amini K, Mojtahedzadeh M, Najmeddin MR, Mohammadi AT, Amini K, Mojtahedzadeh M, *et al.* The Systematic Review and Meta-Analysis of the Efficacy of Granulocyte-Colony Stimulating Factor (G-CSF) in Treatment of Sepsis and Septic Shock. *Comprehensive Health and Biomedical Studies 2024 3:2* 2024;3:e161333.

19. Pinder EM, Rostron AJ, Hellyer TP, Ruchaud-Sparagano MH, Scott J, MacFarlane JG, *et al.* Randomised controlled trial of GM-CSF in critically ill patients with impaired neutrophil phagocytosis. *Thorax* 2018;73:918–925.

20. Shorr AF, Bernard GR, Dhainaut JF, Russell JR, Macias WL, Nelson DR, *et al.* Protein C concentrations in severe sepsis: An early directional change in plasma levels predicts outcome. *Crit Care* 2006;10:1–8.

21. Yan SB, Helterbrand JD, Hartman DL, Wright TJ, Bernard GR. Low Levels of Protein C Are Associated With Poor Outcome in Severe Sepsis. *Chest* 2001;120:915–922.

22. Macias WL, Nelson DR. Severe protein C deficiency predicts early death in severe sepsis. *Crit Care Med* 2004;32:S223-8.

23. Bernard GR, Vincent J-L, Laterre P-F, LaRosa SP, Dhainaut J-F, Lopez-Rodriguez A, *et al.* Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis. *New England Journal of Medicine* 2001;344:699–709.

24. Ranieri VM, Thompson BT, Barie PS, Dhainaut J-F, Douglas IS, Finfer S, *et al.* Drotrecogin Alfa (Activated) in Adults with Septic Shock. *New England Journal of Medicine* 2012;366:2055–2064.

25. Sinha P, Kerchberger E, Willmore A, Chambers J, Zhuo H, Abbott J, *et al.* Identifying molecular phenotypes in sepsis: an analysis of two prospective observational cohorts and secondary analysis of two randomised controlled trials. *Lancet Respiratory Medicine* 2023;11:965–974.

26. Antcliffe DB, Mi Y, Santhakumaran S, Burnham KL, Prevost AT, Ward JK, *et al.* Patient stratification using plasma cytokines and their regulators in sepsis: relationship to outcomes, treatment effect and leucocyte transcriptomic subphenotypes. *Thorax* 2024;79:515–523.

27. Pan B, Sun P, Pei R, Lin F, Cao H. Efficacy of IVIG therapy for patients with sepsis: a systematic review and meta-analysis. *Journal of Translational Medicine 2023 21:1* 2023;21:1–13.

28. Jarczak D, Kluge S, Nierhaus A. Use of Intravenous Immunoglobulins in Sepsis Therapy—A Clinical View. *Int J Mol Sci* 2020;21:5543.

29. Premer C, Hare JM, Yuan SY, Wilson JW. Mesenchymal stem/stromal cells as a therapeutic for sepsis: a review on where do we stand? *Stem Cell Research & Therapy 2025 16:1* 2025;16:1–11.

30. Galstian GM, Parovichnikova EN, Makarova PM, Kuzmina LA, Troitskaya V V., Gemdzhian E, *et al.* The Results of the Russian Clinical Trial of Mesenchymal Stromal Cells (MSCs) in Severe Neutropenic Patients (pts) with Septic Shock (SS) (RUMCESS trial). *Blood* 2015;126:2220–2220.

31. Paterson CW, Fay KT, Chen C-W, Klingensmith NJ, Gutierrez MB, Liang Z, *et al.* CTLA-4 Checkpoint Inhibition Improves Sepsis Survival in Alcohol-Exposed Mice. *Immunohorizons* 2024;8:74.

32. Chang KC, Burnham CA, Compton SM, Rasche DP, Mazuski RJ, SMcDonough J, *et al.* Blockade ofthe negative co-stimulatory molecules PD-1 and CTLA-4 improves survival in primary and secondary fungal sepsis. *Critical Care 2013 17:3* 2013;17:1–14.

33. McBride MA, Patil TK, Bohannon JK, Hernandez A, Sherwood ER, Patil NK. Immune Checkpoints: Novel Therapeutic Targets to Attenuate Sepsis-Induced Immunosuppression. *Front Immunol* 2021;11:624272.