Supplementary material

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Report of Phase Ia COS development: Outcome identification

1. Literature review

1.1 Literature review search strategy

The COS consensus process was informed by a comprehensive search of Medline, Embase via OVID (from inception until 08 September 2023). The search was limited to English-language publications and protocols. Data from research protocols were extracted from two clinical trials registries, Clinical Trials.gov and the International Clinical Trials Registry Platform.

Table Ia-1. Medline search strategy

Database: Ovid MEDLINE(R) ALL <1946 to September 08, 2023> Search Strategy
1. Dengue/ or Severe Dengue/ or Dengue Virus/ (19462)
2. Dengue fever.ab,kf,ti. (6116)
3. DENV.ab,kf,ti. (6217)
4. “Dengue virus*".ab,kf,ti. (12617)
5. Dengue h?emorrhagic fever.ab,kf,ti. (2970)
6. Dengue shock.ab,kf,ti. (1229)
7. Severe dengue.ab,kf,ti. (1544)
8. Breakbone Fever.ab,kf,ti. (13)
9. Break-bone Fever.ab,kf,ti. (19)
10. Thai H?emorrhagic Fever.ab,kf,ti. (24)
11. Philippine H?emorrhagic Fever.ab,kf,ti. (12)
12. Singapore H?emorrhagic Fever.ab,kf,ti. (2)
13. “H?emorrhagic Dengue*".ab,kf,ti. (121)
14. "Dengue infection*".ab,kf,ti. (2881)
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (24906)
16. Clinical Trial/ (538797)
17. Qualitative Research/ (82803)

18. Outcome Assessment, Health Care/ (82287)
19. exp Patient Reported Outcome Measures/ (13927)
20. "patient-reported outcome measure*".ab,kf,ti. (12900)
21. "patient-reported outcome*".ab,kf,ti. (37710)
22. "semi structured interview*".ab,kf,ti. (50754)
23. clinical trial.ab,kf,ti. (202235)
24. randomi?ed clinical trial.ab,kf,ti. (44581)
25. qualitative research.ab,kf,ti. (35403)
26. outcome assessment.ab,kf,ti. (8648)
27. outcome measurement.ab,kf,ti. (5484)
28. "patient experience*".ab,kf,ti. (25194)
29. Patient Satisfaction/ (89683)
30. "patient perception*".ab,kf,ti. (5207)
31. "patient expectation* from treatment".ab,kf,ti. (65)
32. Treatment Outcome/ (1158206)
33. "patient expectation*".ab,kf,ti. (3227)
34. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (2066754)
35. 15 and 34 (554)

Table Ia-2. Embase search strategy

Database: Embase Classic + Embase <1947 to 2023 September 08> Search Strategy	
1	dengue hemorrhagic fever/ or Dengue virus/ or dengue/ or severe dengue/ or dengue shock syndrome/ (35981)
2	Dengue fever.ab,kf,ti. (8289)
3	DENV.ab,kf,ti. (8006)
4	"Dengue virus*".ab,kf,ti. (15917)
5	Dengue h?emorrhagic fever.ab,kf,ti. (4159)
6	Dengue shock.ab,kf,ti. (1740)
7	Severe dengue.ab,kf,ti. (2136)
8	Breakbone Fever.ab,kf,ti. (21)
9	Break-bone Fever.ab,kf,ti. (23)
10	Thai H?emorrhagic Fever.ab,kf,ti. (28)
11	Philippine H?emorrhagic Fever.ab,kf,ti. (20)
12	Singapore H?emorrhagic Fever.ab,kf,ti. (3)
13	H?emorrhagic Dengue*.ab,kf,ti. (151)
14	"Dengue infection*".ab,kf,ti. (4086)
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (39290)
16	clinical trial/ (1090347)
17	semi structured interview/ (61325)
18	outcome assessment/ (859816)
19	patient-reported outcome/ (53561)
20	"patient-reported outcome measure*".ab,kf,ti. (17393)
21	clinical trial.ab,kf,ti. (306577)
22	randomi?ed clinical trial.ab,kf,ti. (59121)
23	qualitative research.ab,kf,ti. (41582)

24 qualitative research/ (118089)

25 outcome assessment.ab,kf,ti. (13720)

26 outcome measurement.ab,kf,ti. (7576)

27 "patient experience*".ab,kf,ti. (42465)

28 patient satisfaction/ (169967)

29 "patient perception*".ab,kf,ti. (8265)

30 "patient expectation* from treatment".ab,kf,ti. (94)

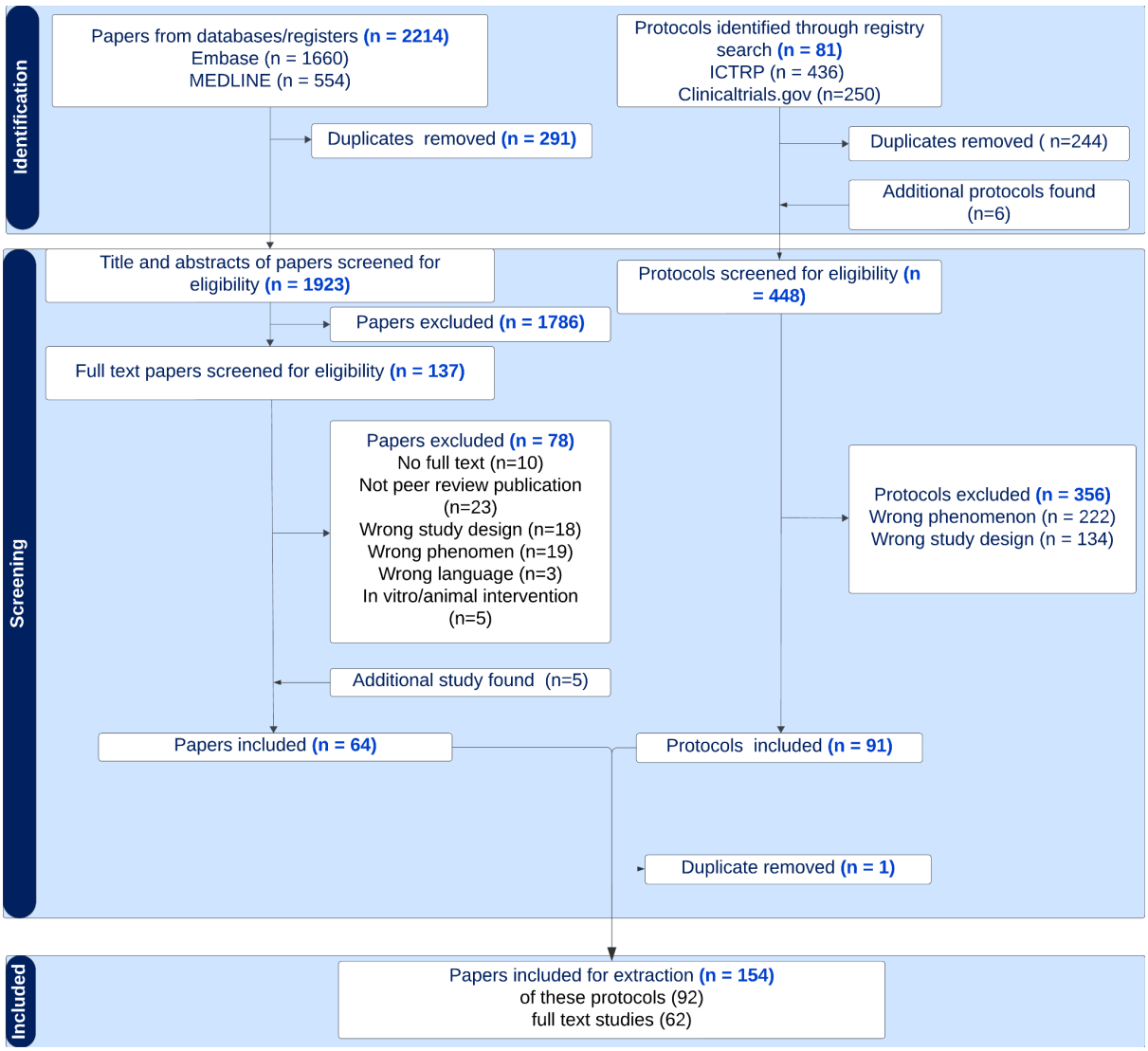
31 expectation/ (33167)

32 treatment outcome/ (968404)

33 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (3229016)

34 15 and 33 (1660)

1.2 PRISMA flowchart



1.3 References for long list of outcomes

Table Ia-3 Included protocols

	Trial Id	Study title
1	NCT06006559	A Study to Assess the Efficacy, Safety and Pharmacokinetics of EYU688 in Patients With Dengue Fever
2	CTRI/2023/07/055129	A comparative study betwwen guduchi kwath and kiratatikta kwath to increase the platelet count in dengue fever
3	CTRI/2023/06/053816	Comparison of 20%Albumin & Crystalloids in Management of Critical Phase of Dengue Fever in Children Between Age Group 1-12years- A Randomized Controlled Trial

4	SLCTR/2023/007	Effect of Vitamin E supplementation on clinical outcomes and related hematological, biochemical, and oxidative stress parameters in 5 – 14-year-old children infected with dengue virus
5	NCT05631405	Efficacy of Dengue Infection With Warning Signs Treated With Dexamethasone (DengDex Study)
6	NCT05611710	Anakinra in Dengue With Hyperinflammation (AnaDen)
7	SLCTR/2022/023	Double Blind Placebo Controlled Randomized Phase III trial to evaluate the efficacy of Eltrombopag to correct thrombocytopenia and prevent fluid leakage in moderate dengue patients
8	NCT05466240	Study of AT-752 in Patients With Dengue Infection
9	NCT02061358	Study to Determine the Safety, Tolerability and Pharmacokinetics of UV-4B Solution Administered Orally in Healthy Subjects (UV)
10	CTRI/2022/04/042131	A Phase 2 randomized, double-blind, placebo-controlled, dose-ranging trial to evaluate pharmacokinetics, pharmacodynamics, and safety of AT-752 in patients with dengue infection
11	SLCTR/2022/003	Dextran in Early Leakage Phase of Dengue Prevents Shock
12	CTRI/2021/09/036661	Role of doxycycline in treatment of dengue infection in adult
13	NCT05034809	Effectiveness Of High Dose Melatonin As Adjunctive Therapy For Dengue Fever With Warning Signs
14	CTRI/2021/07/035290	A Phase II, Single blind, Randomized, Parallel group, Dose ranging, Single Dose Study of Dengue Monoclonal antibody (Dengue mAb) in Adults with Dengue Fever
15	NCT05048875	An Evaluation of Repeated Oral Doses of JNJ-64281802 Against DENV-3 Challenge
16	NCT04906980	A Study of JNJ-64281802 in Participants With Confirmed Dengue Fever
17	NCT04906980	A Study of JNJ-64281802 in Participants With Confirmed Dengue Fever
18	ITMCTR2100004502	Clinical study on the efficacy and safety of ganghuokanggan granule in the treatment of dengue fever
19	NCT04673422	Effect of Montelukast in Preventing Dengue With Warning Signs in Dengue Patients
20	CTRI/2020/11/029254	Role of HPLT031707 SYRUP in low platelet count among children due to varied etiology
21	NCT04597437	Zanamivir Treatment of Vascular Permeability in Dengue (ZAP-DENGUE) (ZAP-DENGUE)
22	TCTR20200916008	Effect of Continuous Positive Airway Pressure on Time to Resolution of Dengue-associated Pleural Effusion
23	TCTR20200506004	A pilot study examining the effect of Kelulut honey versus placebo in dengue infected patients: A randomized controlled trial.
24	NCT04377451	Metformin in Dengue With Obesity (MeDO)
25	NCT05366439	Study of AT-752 in Healthy Subjects in a Dengue Human Challenge Model
26	NCT04273217	A Study to Determine the Safety of AV-1, an Antibody Being Developed for Treatment of Dengue, in Healthy Volunteers
27	CTRI/2020/01/022785	An Open Label, Single Arm Clinical study To Evaluate The Safety and Efficacy of HPLT031707 SYRUP in Cases of Thrombocytopenia Associated With Dengue Fever in Pediatric Population - PL_S

28	CTRI/2020/01/022694	Volume Replacement therapy in children with Dengue: Single centre, Open Labeled, Randomized Control Study to compare the hemodynamic response of two fluid replacement therapy regimen in children presenting with warning signs and compensated shock
29	SLCTR/2019/037	Efficacy and Safety of Eltrombopag to correct thrombocytopenia in moderate to severe dengue patients- a Phase II Randomized Clinical Controlled Trial
30	CTRI/2019/09/021244	CLINICAL EFFECTIVENESS OF ASCORBIC ACID AND THIAMINE AS ADJUNCTIVE THERAPY IN CHILDREN WITH SEVERE DENGUE REQUIRING PICU (PEDIATRIC INTENSIVE CARE UNIT) CARE- OPEN LABELLED RANDOMISED CONTROLLED TRIAL.
31	CTRI/2019/09/021026	Need-based vs guidelines-based fluid administration in dengue patients with warning signs: Open-label randomized study.
32	CTRI/2019/04/018435	Profile of Dengue Fever and effect of carica papaya leaf extract capsule on platelet counts and clinical bleeding
33	NCT03883620	Safety Study of Dengushield in Healthy Adults
34	CTRI/2019/01/017096	An open labeled, randomized, comparative study to evaluate the Effectiveness of GanjhuVirTM a herbal antiviral in Cases of Dengue Fever with Thrombocytopenia
35	CTRI/2018/08/015526	A Multi-centric, Double blind, Prospective, Placebo controlled, Randomized, observational study to evaluate the Efficacy and Safety of Carica Papaya Leaf Extract (CARIMAX), as empirical therapy for prevent Thrombocytopenia associated with Dengue Fever
36	CTRI/2018/07/014988	A Multi-centric, Double blind, Placebo controlled, Randomized, observational study to evaluate the Efficacy and Safety of Carica Papaya Leaf Extract, (ZYBORICA TABLET) as empirical therapy for thrombocytopenia associated with dengue fever
37	CTRI/2018/05/014256	chloride restrictive versus chloride liberal fluid therapy protocol in children aged 2 months-18 years with dengue shock-open label randomised control study
38	CTRI/2018/03/012781	Albumin versus saline for fluid resuscitation in children with severe dengue: A Prospective Randomized Control Trial
39	CTRI/2018/03/012792	Efficacy and Safety of Carica Papaya Leaf Extract in Dengue Fever with Thromobocytopenia in Paediatric age Group
40	CTRI/2018/03/012738	Clinical Evaluation for the Thrombopoietic Activity of Platenza Tablet in Cases of Dengue with Thrombocytopenia- Randomized Open Label Controlled Comparative Clinical Study
41	CTRI/2018/03/012697	Clinical Evaluation for the Thrombopoietic Activity of Platenza Tablet in Cases of Dengue with Thrombocytopenia- Randomized Open Label Comparative Clinical Study
42	CTRI/2018/02/011916	Clinical Evaluation for the Thrombopoietic Activity of Platenza Tablet in Cases of Dengue with Thrombocytopenia- Randomized Open Label Controlled Clinical Study
43	CTRI/2018/02/011789	Clinical Evaluation for Thrombopoietic activity of PLATENZA Tablet in the Cases of Dengue with Thrombocytopenia, Randomized Open Label Comparative Clinical Study
44	CTRI/2018/01/011548	Role of Doxycycline in Management of Children with Dengue Infection
45	ISRCTN35227717	Oseltamivir for treatment of thrombocytopenia and plasma leakage in dengue

46	NCT03432442	Pharmacokinetics and Pharmacodynamics of Ivermectin in Pediatric Dengue Patients (PKIDEN)
47	CTRI/2017/12/010834	Positive Approach Treatment of DENGUE FEVER with Internet Base Searched New Re-purposed Antiviral and Anti-cytokine drugs for Radical Cure
48	CTRI/2017/11/010586	Evaluation of add on efficacy & safety of an ayurvedic formulation in the management of dengue fever & prevention of its complications â€“ A double blind clinical study
49	CTRI/2017/11/010547	Per Rectal Nutritional Integration In Severe Dengue Tertiary Stage
50	SLCTR/2017/037	Efficacy of the combination of oral tranexamic acid with oral norethisterone versus oral tranexamic acid alone in treatment of bleeding per vagina during dengue infection - A single blinded,randomized controlled study
51	SLCTR/2017/034	Effect of papaya (Carica papaya) leaf extract on plasma leakage and platelet count in dengue fever: a randomized controlled trial
52	CTRI/2017/08/009579	A prospective study to evaluate the safety and efficacy of Carica papaya leaf extract (Oral Caripill) in the treatment of severe thrombocytopenia (s30,000/Âµl) in dengue
53	SLCTR/2017/028	Effectiveness of Vitamin C in reducing morbidity in patients with Dengue fever - A double blinded randomized placebo controlled pilot study.
54	CTRI/2017/07/009139	Effectiveness of Carica Papaya leaf extract in increasing the platelet count in cases of dengue fever with thrombocytopenia“ A double blind placebo randomised controlled trial
55	SLCTR/2017/024	The efficacy of rupatadine in reducing the incidence of dengue haemorrhagic fever and complications in patients with dengue fever: a randomised, double blind, placebo controlled trial
56	NCT04076254	Resuscitation With Albumin 5% in Dengue Haemorrhagic Fever
57	ChiCTR-IPR-16009233	Lianbizhi injection for treatment of dengue fever - randomized controlled multicenter clinical study
58	NCT03875560	IC14 in Adult Patients With Dengue Fever
59	NCT02833584	Safety of Paracetamol as Antipyretic in Treatment of Dengue Infection in Adults
60	ISRCTN25394628	The effectiveness of a fluid chart in the outpatient management of suspected dengue cases: a pilot study.
61	TCTR20151110001	randomized controlled trial of zinc supplementation for regulation severity of dengue viral infection in children
62	NCT02673840	Ketotifen as a Treatment for Vascular Leakage During Dengue Fever (KETODEN)
63	NCT02569827	Celgosivir or Modipafant as Treatment for Adult Participants With Uncomplicated Dengue Fever in Singapore
64	ChiCTR-IPR-15006778	Efficacy and safety of Tanreqing injection in patients with dengue fever: a randomised, proof-of-concept trial
65	SLCTR/2015/012	Effects of Vitamin E Supplementation on the clinical outcome of Dengue Fever and Dengue Haemorrhagic Fever in Children
66	CTRI/2015/05/005806	A Multi-centric, Double blind, Placebo controlled, Randomized, observational study to evaluate the Efficacy and Safety of Carica Papaya Leaf Extract, as empirical therapy for thrombocytopenia associated with dengue feverSafety of Carica Papaya Leaf Extract, as empirical therapy for thrombocytopenia associated with dengue fever

67	CTRI/2014/10/005120	EFFECT OF CARICA PAPAYA LEAF EXTRACT ON PLATELET AGGREGATION, MEMBRANE FLUIDITY AND P-SELECTIN EXPRESSION IN DENGUE INFECTION: A RANDOMISED CONTROLLED TRIAL
68	SLCTR/2014/023	Effect of Rupatadine compared to placebo in the reducing complications of acute dengue infection
69	ChiCTR-TRC-14005244	efficacy and safety of ReDuNing Injection in hospitalized uncomplicated Dengue fever patients: a pil
70	CTRI/2014/06/004660	A Prospective, open labeled, clinical study to evaluate the efficacy and safety of DENPAP of liquid syrup in the treatment of Dengue fever
71	NCT02045069	Efficacy and Safety of Ivermectin Against Dengue Infection
72	NCT02016027	Pharmacological Effect of Carica Papaya Leaves Mother Tincture in Healthy Individuals Blood Parameter (CF2013)
73	SLCTR/2013/005	Controlled trial on effect of Carica papaya leaf extract on patients with Dengue Fever
74	ISRCTN03147572	Lovastatin versus placebo for the treatment of dengue in Vietnamese adults
75	NCT01619969	Celgosivir as a Treatment Against Dengue (CELADEN)
76	NCT01601613	Activated Recombinant Human Factor VII in Patients With Dengue Haemorrhagic Fever
77	NCT01443247	Role of Andi-d in Dengue Fever: a Pilot Study
78	NCT01096576	A Study of Balapiravir in Patients With Dengue Virus Infection
79	NCT01030211	Adult Dengue Platelet Study (ADEPT)
80	NCT00966628	Effect of Hypertonic Sodium Lactate on sVCAM-1 Level as Surrogate Marker of Endothelial Capillary Leakage in Pediatric Dengue Shock Syndrome Patients (DSS)
81	NCT00849602	The Effect of Chloroquine in the Treatment of Patients With Dengue
82	ISRCTN39575233	A pilot study to investigate the effects of short course oral corticosteroid therapy in early dengue infection in Vietnamese patients
83	SLCTR/2007/004	Efficacy of Fresh Frozen Plasma (FFP) on thrombocytopaenia in dengue fever
84	ISRCTN38002730	A research study of the role of chloroquine in treating patients with dengue
85	ChiCTR2100043774	Clinical study of ganghuokanggan Decoction on dengue fever
86	ChiCTR-IPR-16009233	Lianbizhi injection for treatment of dengue fever - randomized controlled multicenter clinical study
87	ChiCTR-IPR-15006778	Efficacy and safety of Tanreqing injection in patients with dengue fever: a randomised, proof-of-concept trial
88	NCT06071481	Role of Vitamin D in Prevention of Dengue Haemorrhagic Fever and Dengue Shock Syndrome
89	CTRI/2023/08/056814	Comparison of normal saline vs plasmalyte on serum chloride levels in Dengue Shock Syndrome in children
90	CTRI/2023/11/059752	Efficacy of Montelukast in reducing incidence of warning signs and severe disease in patients with dengue fever: a double-blind, placebo-controlled, randomized trial(MID Trial)
91	CTRI/2022/09/045521	EFFECT OF VITAMIN E & C SUPPLEMENTATION ON THROMBOCYTOPENIA IN DENGUE FEVER

Table Ia-4 Included studies

	Document type	Study title
1	Article	Malavige, G.N. et al. (2022) 'Efficacy of rupatadine in reducing the incidence of dengue haemorrhagic fever in patients with acute dengue: A randomised, double blind, placebo-controlled trial,' PLoS Neglected Tropical Diseases, 16(6), p. e0010123. https://doi.org/10.1371/journal.pntd.0010123.
2	Article	Tunjungputri, R.N. et al. (2022) 'Effect of oseltamivir phosphate versus placebo on platelet recovery and plasma leakage in adults with dengue and thrombocytopenia; a phase 2, multicenter, double-blind, randomized trial,' PLoS Neglected Tropical Diseases, 16(1), p. e0010051. https://doi.org/10.1371/journal.pntd.0010051.
3	Article	Chakraborty, S. et al. (2020) 'Investigation of the efficacy and safety of eltrombopag to correct thrombocytopenia in moderate to severe dengue patients - a phase II randomized controlled clinical trial,' EClinicalMedicine, 29–30, p. 100624. https://doi.org/10.1016/j.eclinm.2020.100624.
4	Article	Vasikasin, V. et al. (2019) 'Effect of standard dose paracetamol versus placebo as antipyretic therapy on liver injury in adult dengue infection: a multicentre randomised controlled trial,' The Lancet Global Health, 7(5), pp. e664–e670. https://doi.org/10.1016/s2214-109x(19)30032-4.
5	Article	Srikanth, B. et al. (2019) ' An open-label, randomized prospective study to evaluate the efficacy and safety of Carica papaya leaf extract for thrombocytopenia associated with dengue fever in pediatric subjects ,' Pediatric Health Medicine and Therapeutics, Volume 10, pp. 5–11. https://doi.org/10.2147/phmt.s176712.
6	Article	Malavige, G.N. et al. (2018) 'A preliminary study on efficacy of rupatadine for the treatment of acute dengue infection,' Scientific Reports, 8(1). https://doi.org/10.1038/s41598-018-22285-x.
7	Article	Ahmad A, Waseem T, Butt NF, Randhawa FA, Malik U, Shakoori TA. Montelukast Reduces the Risk of Dengue Shock Syndrome in Dengue Patients. Trop Biomed. 2018 Dec 1;35(4):1115-1122. PMID: 33601858.
8	Article	Chathurangana, P.W.P. et al. (2017) 'Effects of vitamin E supplementation on the clinical outcome of dengue fever and dengue haemorrhagic fever in children,' Asian Pacific Journal of Tropical Disease, 7(11), pp. 645–649. https://doi.org/10.12980/apjtd.7.2017d7-176.
9	Article	Whitehorn, J. et al. (2015) 'Lovastatin for the treatment of adult patients with dengue: A Randomized, Double-Blind, Placebo-Controlled Trial,' Clinical Infectious Diseases, p. civ949. https://doi.org/10.1093/cid/civ949.
10	Article	Somasetia, D.H. et al. (2014) 'Early resuscitation of dengue shock syndrome in children with hyperosmolar sodium-lactate: a randomized single-blind clinical trial of efficacy and safety,' Critical Care, 18(5). https://doi.org/10.1186/s13054-014-0466-4.
11	Article	Randomized clinical trial of human interleukin-11 in Dengue fever-associated thrombocytopenia (2014). https://pubmed.ncbi.nlm.nih.gov/24613110/.
12	Article	Nguyen, N.M. et al. (2012) 'A randomized, Double-Blind placebo controlled trial of balapiravir, a polymerase inhibitor, in adult dengue patients,' The Journal of Infectious Diseases, 207(9), pp. 1442–1450. https://doi.org/10.1093/infdis/jis470.

13	Article	Borges, M. C., Castro, L. A., & Fonseca, B. A. (2013). Chloroquine use improves dengue-related symptoms. Memorias do Instituto Oswaldo Cruz, 108(5), 596–599. https://doi.org/10.1590/s0074-02762013000500010
14	Article	Castro, J.E.Z. et al. (2011) 'Modulation of Cytokine and Cytokine Receptor/Antagonist by Treatment with Doxycycline and Tetracycline in Patients with Dengue Fever,' Clinical and Developmental Immunology, 2011, pp. 1–5. https://doi.org/10.1155/2011/370872.
15	Article	Kularatne, S. a M. et al. (2009) 'Efficacy of low dose dexamethasone in severe thrombocytopenia caused by dengue fever: a placebo controlled study,' Postgraduate Medical Journal, 85(1008), pp. 525–529. https://doi.org/10.1136/pgmj.2008.078444.
16	Article	De Castro, R.A.C. et al. (2007) 'THROMBOCYTOPENIA ASSOCIATED WITH DENGUE HEMORRHAGIC FEVER RESPONDS TO INTRAVENOUS ADMINISTRATION OF ANTI-D (RH0-D) IMMUNE GLOBULIN,' American Journal of Tropical Medicine and Hygiene, 76(4), pp. 737–742. https://doi.org/10.4269/ajtmh.2007.76.737.
17	Article	Choice of colloidal solutions in dengue hemorrhagic fever patients (2008). https://pubmed.ncbi.nlm.nih.gov/19253503/.
18	Article	Chuansumrit, Ampaiwana; Tangnararatchakit, Kanchanaa; Lektakul, Yujindab; Pongthanapisith, Virojc; Nimjaroenniyom, Nuntapornd; Thanarattanakorn, Pattrae; Wongchanchailert, Malaif; Komwilaisak, Patchareeg. The use of recombinant activated factor VII for controlling life-threatening bleeding in Dengue Shock Syndrome. Blood Coagulation & Fibrinolysis 15(4):p 335-342, June 2004.
19	Article	Khor, C.-S. et al. (2021) 'Lactococcus lactis Strain Plasma Intake Suppresses the Incidence of Dengue Fever-like Symptoms in Healthy Malaysians: A Randomized, Double-Blind, Placebo-Controlled Trial,' Nutrients, 13(12), p. 4507. https://doi.org/10.3390/nu13124507.
20	Article	Salgado, Doris MD*; Zabaleta, Tatiana Esther MD*; Hatch, Steven MD, MSc†; Vega, Marta Rocio MD*; Rodriguez, Jairo MD, PhD*. Use of Pentoxifylline in Treatment of Children With Dengue Hemorrhagic Fever. The Pediatric Infectious Disease Journal 31(7):p 771-773, July 2012. | DOI: 10.1097/INF.0b013e3182575e6a
21	Article	Ackaert, O. et al. (2023) 'Safety, tolerability, and pharmacokinetics of JNJ-1802, a pan-serotype dengue direct antiviral small molecule, in a Phase 1, Double-Blind, randomized, Dose-Escalation study in healthy volunteers,' Clinical Infectious Diseases, 77(6), pp. 857–865. https://doi.org/10.1093/cid/ciad284.
22	Article	Suputtamongkol, Y. et al. (2020) 'Ivermectin accelerates circulating nonstructural protein 1 (NS1) clearance in adult dengue patients: a combined phase 2/3 randomized double-blinded placebo controlled trial,' Clinical Infectious Diseases, 72(10), pp. e586–e593. https://doi.org/10.1093/cid/ciaa1332.
23	Article	Aslam, H. et al. (2021) 'Role of Corticosteroids In Dengue Fever in Pakistan,' Pakistan Journal of Medical and Health Sciences, 15(11). https://doi.org/10.53350/pjmhs2115113014.
24	Article	Sung, C. et al. (2016) 'Extended Evaluation of Virological, Immunological and pharmacokinetic endpoints of CELADEN: A Randomized, Placebo-Controlled trial of Celgosivir in dengue fever patients,' PLoS Neglected Tropical Diseases, 10(8), p. e0004851. https://doi.org/10.1371/journal.pntd.0004851.

25	Article	A Multi-centric, Double-blind, Placebo-controlled, Randomized, Prospective Study to Evaluate the Efficacy and Safety of Carica papaya Leaf Extract, as Empirical Therapy for Thrombocytopenia associated with Dengue Fever (2016). https://pubmed.ncbi.nlm.nih.gov/27739262/.
26	Article	A Multi-centric, Double-blind, Placebo-controlled, Randomized, Prospective Study to Evaluate the Efficacy and Safety of Carica papaya Leaf Extract, as Empirical Therapy for Thrombocytopenia associated with Dengue Fever (2016). https://pubmed.ncbi.nlm.nih.gov/27739262/.
27	Article	Assir, M.Z.K. et al. (2013) 'Effectiveness of platelet transfusion in dengue fever: a randomized controlled trial,' Transfusion Medicine and Hemotherapy, 40(5), pp. 362–368. https://doi.org/10.1159/000354837.
28	Article	Shashidhara, K.C. (2013) 'Effect of High Dose of Steroid on Platelet count in Acute Stage of Dengue Fever with Thrombocytopenia,' JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH [Preprint]. https://doi.org/10.7860/jcdr/2013/6135.3143.
29	Article	Yunita, F., Hanani, E. and Kristianto, J. (2012) The effect of Carica papaya L. leaves extract capsules on platelets count and hematocrit level in dengue fever patient. https://www.semanticscholar.org/paper/The-effect-of-Carica-papaya-L.-leaves-extract-on-in-Yunita-Hanani/c2f47a5b22c1d788db8b5f926e7914a028a8a199.
30	Article	Vaish, A., Verma, S., Agarwal, A., Gupta, L., & Gutch, M. (2012). Effect of vitamin E on thrombocytopenia in dengue fever. Annals of Tropical Medicine and Public Health, 5(4), 282–285. https://doi.org/10.4103/1755-6783.102004
31	Article	Mir M, Khurshid R, Aftab R. Management of thrombocytopenia and flu-like symptoms in dengue patients with herbal water of Euphorbia hirta. J Ayub Med Coll Abbottabad. 2012;24(3-4):6-9.
32	Article	Tricou, V. et al. (2010) 'A randomized controlled trial of chloroquine for the treatment of dengue in Vietnamese adults,' PLoS Neglected Tropical Diseases, 4(8), p. e785. https://doi.org/10.1371/journal.pntd.0000785.
33	Article	Pohan HT, Lie KC, Santoso WD, Eppy. An open pilot study of the efficacy and safety of Polygeline in adult subjects with dengue haemorrhagic fever. Acta Med Indones. 2009;41(2):47-53.
34	Article	Dimaano EM, Saito M, Honda S, et al. Lack of efficacy of high-dose intravenous immunoglobulin treatment of severe thrombocytopenia in patients with secondary dengue virus infection. Am J Trop Med Hyg. 2007;77(6):1135-1138.
35	Article	Sellahewa KH, Samaraweera N, Thusita KP, Fernando JL. Is fresh frozen plasma effective for thrombocytopenia in adults with dengue fever? A prospective randomised double blind controlled study. Ceylon Med J. 2008;53(2):36-40. doi:10.4038/cmj.v53i2.229
36	Article	Jacobs J, Fernandez EA, Merizalde B, Avila-Montes GA, Crothers D. The use of homeopathic combination remedy for dengue fever symptoms: a pilot RCT in Honduras. Homeopathy. 2007;96(1):22-26. doi:10.1016/j.homp.2006.10.004
37	Article	Wills BA, Nguyen MD, Ha TL, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med. 2005;353(9):877-889. doi:10.1056/NEJMoa044057
38	Article	Chuansumrit A, Wangruangsatid S, Lektrakul Y, et al. Control of bleeding in children with Dengue hemorrhagic fever using recombinant activated factor VII: a randomized, double-blind, placebo-controlled study. Blood Coagul Fibrinolysis. 2005;16(8):549-555. doi:10.1097/01.mbc.0000186837.78432.2f

39	Article	Cam BV, Tuan DT, Fonsmark L, et al. Randomized comparison of oxygen mask treatment vs. nasal continuous positive airway pressure in dengue shock syndrome with acute respiratory failure. J Trop Pediatr. 2002;48(6):335-339. doi:10.1093/tropej/48.6.335
40	Article	Ngo NT, Cao XT, Kneen R, et al. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis. 2001;32(2):204-213. doi:10.1086/318479
41	Article	Dung NM, Day NP, Tam DT, et al. Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. Clin Infect Dis. 1999;29(4):787-794. doi:10.1086/520435
42	Article	Sathyapalan, D.T. et al. (2020) 'Efficacy & safety of Carica papaya leaf extract (CPLE) in severe thrombocytopenia (≤30,000/μl) in adult dengue – Results of a pilot study,' PLoS ONE, 15(2), p. e0228699. https://doi.org/10.1371/journal.pone.0228699.
43	Article	Lye, D.C. et al. (2017) 'Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopenia: a multicentre, open-label, randomised, superiority trial,' The Lancet, 389(10079), pp. 1611–1618. https://doi.org/10.1016/s0140-6736(17)30269-6.
44	Article	Nainggolan, L., Bardosono, S. and Ilyas, E.I.I. (2018) 'The tolerability and efficacy of oral isotonic solution versus plain water in dengue patients: A randomized clinical trial,' Indian Journal of Community Medicine, 43(1), p. 29. https://doi.org/10.4103/ijcm.ijcm_377_16.
45	Article	Fredeking TM, Zavala-Castro JE, González-Martínez P, et al. Dengue Patients Treated with Doxycycline Showed Lower Mortality Associated to a Reduction in IL-6 and TNF Levels. Recent Pat Antiinfect Drug Discov. 2015;10(1):51-58. doi:10.2174/1574891x10666150410153839
46	Article	Low, J.G. et al. (2014) 'Efficacy and safety of celgosivir in patients with dengue fever (CELADEN): a phase 1b, randomised, double-blind, placebo-controlled, proof-of-concept trial,' The Lancet Infectious Diseases, 14(8), pp. 706–715. https://doi.org/10.1016/s1473-3099(14)70730-3.
47	Article	Reddy, K.R.B.K., Basavaraja, G.V. and Shivananda, N. (2014) 'Furosemide infusion in children with dengue fever and hypoxemia,' Indian Pediatrics, 51(4), pp. 303–305. https://doi.org/10.1007/s13312-014-0398-8.
48	Article	Tam, D.T.H. et al. (2012) 'Effects of Short-Course oral corticosteroid therapy in early dengue infection in Vietnamese patients: a Randomized, Placebo-Controlled trial,' Clinical Infectious Diseases, 55(9), pp. 1216–1224. https://doi.org/10.1093/cid/cis655.
49	preprint	"A COMPARATIVE STUDY OF GUDUCHI KWATH AND CAP.PLATBOOST TO INCREASE THE PLATELET COUNT IN DENGUE FEVER' (no date) International Journal of Sceintific Research [Preprint]. https://doi.org/10.36106/ijsr.
50	Article	Shinde, D. L., Sathe, A., & Mohite, Y. (2021). Comparative study on efficacy of Kiratatikta Kwath and conventional treatment to increase the platelet count in dengue fever. International Journal of All Research Education and Scientific Methods (IJARESM), 9(11), 623–632. Available at: www.ijaresm.com

51	Article	Ha, S. et al. (2018) 'Clinical Evaluation for the Thrombopoietic Activity of Platenza Tablet in Cases of Dengue with Thrombocytopenia - Randomized Open Label Comparative Clinical Study,' Annals of Medical and Health Sciences Research, 8(2). https://www.amhsr.org/articles/clinical-evaluation-for-the-thrombopoietic-activity-of-platenza-tablet-in-cases-of-dengue-with-thrombocytopenia--randomi.pdf.
52	Article	Pambhar, V. et al. (2022) 'Effect of doxycycline and doxycycline with carica papaya on thrombocytopenia and leucopenia in acute dengue fever patients,' Journal of Family Medicine and Primary Care, 11(6), pp. 3270–3275. https://doi.org/10.4103/jfmpc.jfmpc_53_22.
53	Article	Jones, A.M. et al. (2023) 'Measuring dengue illness intensity: Development and content validity of the dengue virus daily diary (DENV-DD),' Journal of Patient-Reported Outcomes, 7(1). https://doi.org/10.1186/s41687-023-00624-5.
54	Article	Ng, W.L. et al. (2023) 'Self-care practices and health-seeking behaviours in patients with dengue fever: A qualitative study from patients' and physicians' perspectives,' PLoS Neglected Tropical Diseases, 17(4), p. e0011302. https://doi.org/10.1371/journal.pntd.0011302.
55	Article	Piroonamornpun, P. et al. (2022) 'Treatment-Seeking Behaviors and Knowledge, Attitude and Practices among Suspected Dengue Adult Patients at the Hospital for Tropical Diseases, Bangkok, Thailand,' International Journal of Environmental Research and Public Health, 19(11), p. 6657. https://doi.org/10.3390/ijerph19116657.
56	Article	Wong, L.P. and AbuBakar, S. (2013) 'Health Beliefs and Practices related to dengue fever: a focus group study,' PLoS Neglected Tropical Diseases, 7(7), p. e2310. https://doi.org/10.1371/journal.pntd.0002310.
57	Article	Margarita, T.L.T. et al. (2006) Cultural Conceptions about Dengue in Nayarit , Mexico. https://iris.who.int/handle/10665/170268?locale-attribute=fr&locale=ar.
58	Article	Xu, J.-W. et al. (2020) 'The health beliefs, dengue knowledge and control behaviors among internally displaced persons versus local residents in Kachin Special Region II, Myanmar,' PLoS Neglected Tropical Diseases, 14(6), p. e0008321. https://doi.org/10.1371/journal.pntd.0008321.
59	Article	Octaviana, D., & Wijayanti, S. P. M. (2019). Community perception to risk of dengue infection and treatment seeking behaviour. Annals of Tropical Medicine and Public Health, 22(11), S316. https://doi.org/10.36295/ASRO.2019.221110
60	Article	Okanurak K, Sornmani S, Mas-ngammueng R, Sitaputra P, Krachangsang S, Limsomboon J. Treatment seeking behavior of DHF patients in Thailand. Southeast Asian J Trop Med Public Health. 1997;28(2):351-358.
61	Article	Kumaran, E. et al. (2018) 'Dengue knowledge, attitudes and practices and their impact on community-based vector control in rural Cambodia,' PLoS Neglected Tropical Diseases, 12(2), p. e0006268. https://doi.org/10.1371/journal.pntd.0006268.
62	Article	Tassniyom, S. et al. (1997) 'Failure of carbazochrome sodium sulfonate (AC-17) to prevent dengue vascular permeability or shock: A randomized, controlled trial,' The Journal of Pediatrics, 131(4), pp. 525–528. https://doi.org/10.1016/s0022-3476(97)70055-6.

2.Qualitative interviews

Qualitative interviews with dengue patient representatives to inform the long list of outcomes.

Interviewees	Adult patients (N=7)	Pediatric patients (N=7)
Male	3	3
Female	4	4

Part A. Illness experience

Adult patients' experience with Dengue	Pediatric patients' experience with Dengue
• Most patients' illnesses started with high fever (38-40oC). Although some took antipyretics, fluid infusions, and wiped the body to reduce the fever, they still got fever again. • The patients often stayed home for 2-3 days before visiting the doctors. They visited doctors when they had a continuous fever for several days despite fever treatments, or when they started vomiting or had severe headaches. Before referring to HTD, some patients were suspected of Dengue because they had family members diagnosed with Dengue recently, or when their platelet counts were below the normal range • Some patients went to HTD directly, while others were referred by doctors at private clinics. They were admitted to the hospital when they got confirmed tests for Dengue at HTD. • All patients stayed in the hospital for a week. • Having dengue impact patients' life: Due to hospitalization, all patients were absent from work or school. For	• Most patients' illnesses started with high fever (38-40oC). Although some took antipyretics, fluid infusions, and wiped the body to reduce the fever, they still got fever again. • The patients often stayed home for 2-3 days before visiting the doctors. They visited doctors when they had a continuous fever for several days despite fever treatments, or when they started vomiting or had severe headaches. Before referring to HTD, some patients were suspected of Dengue because they had family members diagnosed with Dengue recently, or when their platelet counts were below the normal range • Some patients went to HTD directly, while others were referred by doctors at private clinics. They were admitted to the hospital when they got confirmed tests for Dengue at HTD. • All patients stayed in the hospital for a week. • Having dengue impact patients' life: Due to hospitalization, all patients were absent from work or school. For working people, their absence from

working people, their absence from work had some impacts on their income, but they were not significant. Patients who were students indicated that their absence from school had no significant impacts, except for one patient missing the exams due to hospitalization. ● The most bothersome about having Dengue was fever and fatigue, which made the patients uncomfortable and tired. They slept a lot and could not move or do anything.	work had some impacts on their income, but they were not significant. Patients who were students indicated that their absence from school had no significant impacts, except for one patient missing the exams due to hospitalization. ● The most bothersome about having Dengue was fever and fatigue, which made the patients uncomfortable and tired. They slept a lot and could not move or do anything.

Part B. Opinions on outcomes

Adult patients' opinions on outcome	Relatives of patients' opinions on outcome
• The most burdensome symptom of dengue among adult patients was fever, leading to fatigue and sleeping a lot. Accompany to fever, the patients also had headaches and body aches or muscle pains. To deal with fever, the patients took antipyretics, fuild infusion, wiped their bodies, and drank more water. However, they felt that these fever treatments did not work well because they got fevers again after a few hours. Thus, they decided to visit the doctors or HTD after 2-3 days of continuous fever. After hospitalization, the fever symptoms were reduced, and they felt better. • The second burdensome symptom of dengue among adult patients was nausea, vomiting, and lost appetite. One patient mentioned insomnia due to bloating and indigestion. Vomiting and severe stomachaches were the triggers for the patients to visit the doctors. After hospitalization, some patients have been prescribed medication to reduce nausea, but most of them just took a rest and ate small meals with porridge.	• The patients' parents indicated that the most burdensome symptom of dengue was fever. Although most patients did not have high fevers at the beginning of the illness, they got high fevers during their hospitalization and were transferred to the Pediatric ICU. The fact that patients staying in the PICU upset their parents because they could not meet their children often during their stays there. • Vomiting, nausea, and lost appetite were the second most burdensome symptoms of dengue. Because the patients did not want to eat or drink, their parents put a lot of effort into making them eat or drink

The most important factor in the management of dengue	
• Healthcare facilities include rooms with space for moving or exercising in the hospital. • Diet: During illness, some patients felt they lost their appetite. Thus, they believed it was important to pay attention to diet, including eating small meals to reduce the impact of nausea and avoiding eating black and red meats. Additionally, they mentioned drinking more water and wiping the body to cool down during the fever process. • Visiting the hospital as soon as possible to avoid the severe process of disease. • Recovery from dengue illness: All patients felt better than the previous visit but did not fully recover. Some patients indicated that they could work and do physical exercises as usual, while others felt weaker or exhausted after 8 working hours. They also had some symptoms, such as hair loss, muscle pains, lost appetite, and being more sensitive to caffeine (in tea or coffee).	• Instead of taking medication prescribed by the pharmacist at the drug store, the parents should take the patients to the doctor as soon as possible. • Getting the confirmed test as soon as possible: The doctors could distinguish it from other diseases and give the patients the proper treatment. • Diet: Drinking a lot of water and milk. Drinking more water could help patients avoid severe progress of the disease (preventing the condensation in blood and preventing transfer to the PICU). • Caregivers: because the patient got high fevers, the caregivers need to take care of the patient seriously to prevent convulsion. • Cleaning the house and surrounding areas to prevent mosquitoes -> avoiding transmitting to their family members. • Recovery from dengue illness: Most patients recovered and ate as usual. Two patients indicated that they did not run or do exercises as they used to.

Part C. Future research/treatment

If there was a new medication developed for treatment of dengue, what would you hope its effect would be?
• Stop fever and related symptoms such as headache and muscle pains • Increase the platelet count to prevent hospitalization. • Increase coagulation because dengue can cause bleeding • Therapeutical treatment, specifically for Dengue, to help the patients recover quicker • Vaccines to prevent diseases and drugs to prevent severe Dengue. However, the medication should be tested to ensure that it does not have any side effects.
If there was a future program/study on dengue treatment, what would you hope it would achieve?

- Vaccination programs to prevent dengue virus: All patients and their parents have positive attitudes toward Dengue vaccines. However, the vaccines should be tested to ensure safety.
- Dengue virus control and prevention: mosquitoes spray periodically and remove water containers to prevent mosquitoes from laying eggs
- Health education and promotion about the origin of Dengue and disease prevention. Many people do not understand the cause and treatment of the disease, leading to untrust to the doctor's treatment process.
- Nutrition and diet during sickness time.

3. Long list of outcomes for the Delphi survey.

Domain by Dodd et al	Consolidated outcome	Definition used in Delphi survey	Example of individual outcomes
Mortality/survival	Mortality/ Survival	Survival beyond acute dengue illness	30-day mortality; High mortality rate; Mortality
Physiological/clinical	Platelet count	Refers to measuring the number of platelets in a person's blood. Platelets are cells that help our blood clot to stop bleeding. A normal platelet count is important as it helps prevent excessive bleeding or clotting. The count is measured by a blood test and is expressed as the number of platelets per volume of blood. A low platelet count is commonly seen in dengue, known as thrombocytopenia and can increase the risk of bleeding and bruising.	PLT count (Increase, Decrease, Time to reach certain amount, Mean platelet count)
Physiological/clinical	Severe gastrointestinal symptoms	New onset or the worsening of problems related to the gastrointestinal tract, which includes the stomach and intestines. These symptoms can include persistent nausea (feeling like you need to vomit), vomiting more than twice a day, or ongoing diarrhoea (loose, watery stools), and abdominal tenderness.	Diarrhea; Nausea; Persistent vomiting; Vomiting; Loss of taste; Loss of appetite;
Physiological/clinical	Fatigue	New onset or worsening in severity or duration of feeling exhausted, having too little energy, or needing more rest during acute dengue illness	Feeling faint; Feeling tired
Physiological/clinical	Recovery	Recovery refers to the period during which a person regains their health and well-being after experiencing an illness or medical treatment. This process includes disappearance of symptoms, the body's return to its regular functioning, and the ability to engage in everyday tasks and activities. Recovery encompasses	Intensity and duration of symptoms; Clinical symptoms of dengue fever; Duration of the disease; Clinical cure rate; Recovery rate; 100% Recovery; Partial recovery; Relieve of DF symptoms; Main

		not only the physical healing but also the mental and emotional adjustment to life after the illness, leading back to a normal or a new normal state.	symptoms disappeared; Time from fever onset to clinical recovery; Rate of main symptoms disappeared; Symptoms return after cessation of treatment; Symptomatic Relief;
Physiological/clinical	Pain	New or worsening feelings of hurt including aches, stinging, throbbing, or burning that could be sharp or dull, and constant or variable. (e.g headache, muscle pain, joint pain, abdominal pain, etc)	Retro-orbital pain; Ear pain; Eye pain; Severe abdominal pain; Abdominal tenderness or pain; Mouth pain; Reduction in the intensity of pain; Unspecified pain; Aching bones; Arm pain; Back pain; Joint pain; Leg pain; Muscle pain; Shoulder pain; Waist pains; Body ache; Side pain; Kidney pain; Bladder pain; Headache
Physiological/clinical	Fever	New onset or worsening of problems related to the body temperature (e.g. fever that comes and goes, chills or shivers, feeling too cold or too hot).	Time between fever onset and defervescence; Time from fever onset to the first of two consecutive negative viremia; Time of complete fever reduction after treatment; Fever clearance time; Duration and intensity fever; Feeling warmer or hotter; Feeling cold; Shivering/shaking Shivering/shaking; Fever
Physiological/clinical	Viremia/Viral load	The amount of virus present in the blood plasma of an individual. When someone is infected with a virus, that virus can multiply inside their body. The viral load measurement tells doctors how many virus particles are circulating in the blood.	Change in viral load; Viral Load (VL) Curve - AUCD1-D5 [log10VL]); Serum dengue virus load; Viral load AUC for viremia; Detectable viremia level; Area under the log10-transformed viremia curves; Median time to first viremia level of <1000 copies/mL; Peak of detectable viremia level; Presence of detectable

			viremia; Time of first onset of detectable viremia; Time to undetectable viremia;
Physiological/clinical	Development of shock	Shock is a severe medical emergency where the body's circulatory system fails to provide sufficient blood flow, resulting in not enough oxygen being delivered to the cells. This can occur for a variety of reasons, but in dengue this usually results from increased permeability of blood vessels, resulting in leakage of plasma out of the vessels. Shock can be recognized by at least two of the following signs: signs of poor blood flow (hypoperfusion), skin that is cold and clammy, and a rapid but weak pulse; confusion or changes in how alert someone is (altered mental status); pulse pressure (the difference between the systolic and diastolic blood pressure readings) that is narrow (20mmHg or less); low blood pressure for the person's age; and a fast heart rate (over 100 beats per minute). Each of these symptoms points to the body's struggle to maintain blood flow and oxygen supply to vital organs, highlighting the need for urgent medical intervention.	Development of hypotensive shock; Development of shock; Duration of shock; Shock; Reduction of compensated proportion shock by 15%; Reduction of proportion of uncompensated shock by 15%; Blood pressure; Mean arterial pressure (MAP); Hypotension; Pulse pressure improvement; Hemodynamic stabilization; Heart rate; Pulse rate reduction; Rapid heartbeat; Resolution of postural tachycardia; Tachycardia
Physiological/clinical	Organ failure	Organ failure is a critical medical condition where one or more of the body's vital organs stop working correctly. This can involve major organs like the heart, liver, kidneys, or lungs, leading to severe, life-threatening complications. For instance, severe heart failure significantly limits how much physical activity a person can do, while respiratory failure may make it hard to breath and require the use of additional oxygen or assisted ventilation. Kidney failure could mean needing regular dialysis (a treatment to remove waste from the blood when the kidneys can't). The onset of organ failure indicates a serious decline in health, requiring immediate medical attention to support the organs and prevent life threatening complications.	Severe heart involvement; Severe other organ involvement; Severity of illness; Acute liver failure; Severe liver involvement; Liver failure; Derangement of liver transaminases; Liver parameters improvement; Highest AST/ALT; Hematuria; New-onset AKI
Physiologic	Severe fluid	Severe leakage leading to fluid accumulation refers to the	Fluid leakage; Reduction in DHF

al/clinical	leakage	excessive buildup of fluid in different parts of the body, leading to conditions such as peripheral edema (swelling of the lower limbs due to fluid retention), pleural effusion (fluid around the lungs), ascites (fluid in the abdomen), or pericardial effusion (fluid around the heart). These conditions can be identified through physical exams, imaging techniques like X-rays or ultrasound, indicating a significant accumulation of fluid. Importantly, this outcome highlights the presence of severe fluid buildup without it necessarily causing respiratory distress (difficulty breathing) or hemodynamic compromise (problems with blood flow).	development (fluid leakage); Ascites; Plasma leakage; Occurrence of plasma leaking; Pleural effusion

Physiological/clinical	Severe Bleeding	This refers to bleeding or haemorrhage that requires medical intervention. Defined as bleeding resulting in haemodynamic compromise or bleeding that necessitates an intervention, for example a transfusion (donated blood is given to the affected person to replace what they have lost).	Menorrhagia; Menorrhagia or inter-menstrual bleed not controlled by progesterone; Reduction in the quantity of per vaginal bleeding; Vaginal bleeding; Progression to severe bleeding; Bleeding; Overt bleeding; Clinical bleeding excluding petechiae; Bleeding episode completely stopped; Abatement of bleeding manifestation; Time to cessation of bleeding; Bleeding episode decreased; Bleeding episode worsened, remained unchanged, recurred or occurred at a new site; Bleeding had worsen; Bleeding reccurence; Continuation of bleeding; Severe bleeding; Clinically significant bleeding; Intracranial bleed; Internal bleeding; Need in standard haemostatic replacement therapy; GI bleeding; Haematemesis; Haematemesis or melaena not controlled by endoscopic procedure; Hematochezia

Life impact	Health-related Quality of life	This is a broad concept that reflects how a person views the impact of acute dengue illness and its management on their life. It encompasses several key areas: physical well-being, mental and emotional health, and social connections. Specifically in the context of acute dengue illness, Health-related QoL is about understanding how a person feels about their ability to perform daily activities, maintain physical health, manage the emotional stresses brought on by the illness, and engage in meaningful social interactions.	Mobility, Self-care; Sleep related relationships problems; Usual activities (work, study, housework, family, leisure activities); Panic; Irritability; General wellbeing due to the poor sleep; Sleep related mood problems; Difficult with concentration; Sleep related concentration problems; Sleep related productivity problems; Perceived helpfulness; Feeling unwell; Overall improvement; Overall well-being; Quaility of life; Significant improvement in the quality of life
Resource use	Require care at the high dependency unit and/or in the ICU/ITU	A requirement of a higher level of medical attention. This includes care in high dependency units with wards for people who need more intensive observation, treatment and nursing care than is possible in a general ward. In more critical cases, care in an Intensive Care Unit (ICU) or Intensive Therapy Unit (ITU). The ICU/ITU is a specialised department within the hospital designed for patients with life-threatening conditions, offering continuous monitoring and support for vital organ functions (like breathing or blood pressure). This level of care is necessary when someone's health condition is severe, needing advanced treatments and close observation that only a hospital or intensive care environment can provide.	

Report of Phase Ib COS development: Outcome Voting.

Table Ib-1. Consensus criteria used in Delphi and consensus meetings.

Consensus classification	Description	Definition
Consensus in	Consensus that outcome should be included in the core outcome set	70% or more of participants in each group rating the outcome 7-9
Consensus out	Consensus that outcome should not be included in the core outcomes set	50% or fewer in each group scoring 7-9
No consensus	Uncertainty about importance of outcome	Anything else

1. Delphi process

1.1 Table Ib-2 Full details of Delphi participants. Delphi round 1

Characteristic	All participants	Participants by group			
	N = 291[1]	People with lived experience	Healthcare professionals, researchers with lived experience	Healthcare professionals, researchers without lived experience	Representatives of other dengue stakeholders
		N = 48[1]	N = 64[1]	N = 162[1]	N = 17[1]
Age group					
18-29	50 (17%)	20 (42%)	13 (20%)	17 (10%)	0 (0%)
30-39	81 (28%)	14 (29%)	20 (31%)	41 (25%)	6 (35%)
40-49	80 (27%)	7 (15%)	14 (22%)	55 (34%)	4 (24%)
50-59	48 (16%)	4 (8.3%)	10 (16%)	29 (18%)	5 (29%)
60-69	29 (10.0%)	3 (6.3%)	5 (7.8%)	19 (12%)	2 (12%)
70-79	3 (1.0%)	0 (0%)	2 (3.1%)	1 (0.6%)	0 (0%)
Gender					
Female	153 (53%)	29 (60%)	36 (56%)	79 (49%)	9 (53%)
Male	135 (46%)	19 (40%)	28 (44%)	80 (49%)	8 (47%)
Prefer not to say / other	3 (1.0%)	0 (0%)	0 (0%)	3 (1.8%)	0 (0%)
Country of residence					
Argentina	1 (0.3%)	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)
Australia	2 (0.7%)	0 (0%)	0 (0%)	1 (0.6%)	1 (5.9%)

Bangladesh	2 (0.7%)	0 (0%)	1 (1.6%)	0 (0%)	1 (5.9%)
Bolivia	3 (1.0%)	0 (0%)	0 (0%)	3 (1.9%)	0 (0%)
Brazil	14 (4.8%)	3 (6.3%)	5 (7.8%)	6 (3.7%)	0 (0%)
Cambodia	1 (0.3%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
Cameroon	1 (0.3%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
China	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)
Colombia	40 (14%)	18 (38%)	3 (4.7%)	18 (11%)	1 (5.9%)
Egypt	5 (1.7%)	0 (0%)	0 (0%)	4 (2.5%)	1 (5.9%)
Gambia	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)
Germany	1 (0.3%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
Ghana	2 (0.7%)	0 (0%)	0 (0%)	2 (1.2%)	0 (0%)
Honduras	3 (1.0%)	0 (0%)	0 (0%)	0 (0%)	3 (18%)
India	10 (3.4%)	0 (0%)	2 (3.1%)	7 (4.3%)	1 (5.9%)
Indonesia	17 (5.8%)	1 (2.1%)	3 (4.7%)	13 (8.0%)	0 (0%)
Japan	2 (0.7%)	0 (0%)	1 (1.6%)	1 (0.6%)	0 (0%)
Jordan	1 (0.3%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
Lao People's Democratic Republic	2 (0.7%)	0 (0%)	0 (0%)	2 (1.2%)	0 (0%)
Malaysia	21 (7.2%)	1 (2.1%)	2 (3.1%)	17 (10%)	1 (5.9%)
Nepal	7 (2.4%)	0 (0%)	0 (0%)	6 (3.7%)	1 (5.9%)
Netherlands	1 (0.3%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
Pakistan	10 (3.4%)	1 (2.1%)	0 (0%)	9 (5.6%)	0 (0%)
Peru	26 (8.9%)	4 (8.3%)	9 (14%)	12 (7.4%)	1 (5.9%)
Philippines	13 (4.5%)	5 (10%)	4 (6.3%)	4 (2.5%)	0 (0%)
Qatar	1 (0.3%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)

Singapore	22 (7.6%)	3 (6.3%)	6 (9.4%)	13 (8.0%)	0 (0%)
Sri Lanka	21 (7.2%)	0 (0%)	9 (14%)	12 (7.4%)	0 (0%)
Sudan	1 (0.3%)	0 (0%)	1 (1.6%)	0 (0%)	0 (0%)
Switzerland	4 (1.4%)	0 (0%)	0 (0%)	2 (1.2%)	2 (12%)
Syrian Arab Republic	1 (0.3%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
Thailand	4 (1.4%)	0 (0%)	2 (3.1%)	2 (1.2%)	0 (0%)
United Kingdom of Great Britain and Northern Ireland	8 (2.7%)	1 (2.1%)	2 (3.1%)	5 (3.1%)	0 (0%)
United States of America	6 (2.1%)	1 (2.1%)	3 (4.7%)	2 (1.2%)	0 (0%)
Venezuela	1 (0.3%)	0 (0%)	0 (0%)	1 (0.6%)	0 (0%)
Viet Nam	35 (12%)	9 (19%)	11 (17%)	13 (8.0%)	2 (12%)
Experience of dengue					
Hospitalisation for dengue management	69 (58%)	37 (77%)	31 (48%)		1 (17%)
Intensive Care Unit (ICU) Treatment	15 (13%)	11 (23%)	4 (6.3%)		0 (0%)
Outpatient management for uncomplicated dengue	34 (29%)	0 (0%)	29 (45%)		5 (83%)
Age of family member who experienced dengue					
0-5	4 (7.7%)	1 (6.7%)	3 (9.7%)		0 (0%)
5-17	13 (25%)	5 (33%)	7 (23%)		1 (17%)
18-29	9 (17%)	3 (20%)	4 (13%)		2 (33%)
30-39	7 (13%)	1 (6.7%)	5 (16%)		1 (17%)
40-49	6 (12%)	3 (20%)	1 (3.2%)		2 (33%)
50-59	6 (12%)	1 (6.7%)	5 (16%)		0 (0%)
60-69	5 (9.6%)	0 (0%)	5 (16%)		0 (0%)
80-90	2 (3.8%)	1 (6.7%)	1 (3.2%)		0 (0%)

Research focus					
Basic science	15 (5.2%)		3 (4.7%)	12 (7.4%)	0 (0%)
Clinical research	152 (52%)		36 (56%)	109 (67%)	7 (41%)
Epidemiology and Public health	40 (14%)		14 (22%)	18 (11%)	8 (47%)
Other	14 (4.8%)		0 (0%)	13 (8%)	1 (5.9%)
Clinical specialization					
In primary care / family medicine	24 (8.2%)		9 (14%)	13 (8.0%)	2 (12%)
Secondary care / specialty medicine - Infectious and Tropical Diseases	42 (14,4%)		10 (15,6%)	32 (19,7%)	0 (0%)
Secondary care / specialty medicine - Internal medicine	18 (6%)		5 (7,8%)	13 (8%0	0 (0%)
Secondary care / specialty medicine - Paediatric Medicine	13 (4.5%)		3 (4.7%)	10 (6.2%)	0 (0%)
Secondary care / specialty medicine - Critical care	19 (6,5%)		2 (3%)	17 (10,5%)	0 (0%)
Secondary care / specialty medicine (not specified)	17 (5.5%)		6 (7.8%)	10 (6.2%)	1 (5.9%)
Secondary care / specialty medicine (other)	24 (8,25%)		7 (11%)	17 (10,5%)	0 (0%)

1.1 Table Ib-3 Full details of Delphi participants. Delphi round 2

Characteristic	All participants	Participants by group			
	N = 160[1]	People with lived experience	Healthcare professionals, researchers with lived experience	Healthcare professionals, researchers without lived experience	Representatives of other dengue stakeholders
		N = 17[1]	N = 37[1]	N = 97[1]	N = 9[1]
Age group					
18-29	17 (11%)	3 (18%)	5 (14%)	9 (9.3%)	0 (0%)
30-39	45 (28%)	7 (41%)	15 (41%)	21 (22%)	2 (22%)
40-49	48 (30%)	4 (24%)	5 (14%)	36 (37%)	3 (33%)
50-59	30 (19%)	1 (5.9%)	7 (19%)	19 (20%)	3 (33%)
60-69	18 (11%)	2 (12%)	3 (8.1%)	12 (12%)	1 (11%)
70-79	2 (1.3%)	0 (0%)	2 (5.4%)	0 (0%)	0 (0%)
Gender					
Female	78 (49%)	8 (47%)	20 (54%)	45 (46%)	5 (56%)
Male	82 (51%)	9 (53%)	17 (46%)	52 (54%)	4 (44%)
Country of residence					
Argentina	1 (0.6%)	1 (5.9%)	0 (0%)	0 (0%)	0 (0%)
Australia	1 (0.6%)	0 (0%)	0 (0%)	1 (1.0%)	0 (0%)
Bangladesh	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	1 (11%)
Bolivia	2 (1.3%)	0 (0%)	0 (0%)	2 (2.1%)	0 (0%)
Brazil	10 (6.3%)	2 (12%)	3 (8.1%)	5 (5.2%)	0 (0%)
Cambodia	1 (0.6%)	0 (0%)	0 (0%)	1 (1.0%)	0 (0%)

China	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)	1 (11%)
Colombia	13 (8.1%)	0 (0%)	1 (2.7%)	12 (12%)	0 (0%)
Egypt	3 (1.9%)	0 (0%)	0 (0%)	3 (3.1%)	0 (0%)
Ghana	1 (0.6%)	0 (0%)	0 (0%)	1 (1.0%)	0 (0%)
Honduras	2 (1.3%)	0 (0%)	0 (0%)	0 (0%)	2 (22%)
India	4 (2.5%)	0 (0%)	1 (2.7%)	2 (2.1%)	1 (11%)
Indonesia	12 (7.5%)	1 (5.9%)	3 (8.1%)	8 (8.2%)	0 (0%)
Japan	2 (1.3%)	0 (0%)	1 (2.7%)	1 (1.0%)	0 (0%)
Malaysia	13 (8.1%)	1 (5.9%)	0 (0%)	12 (12%)	0 (0%)
Nepal	4 (2.5%)	0 (0%)	0 (0%)	3 (3.1%)	1 (11%)
Pakistan	5 (3.1%)	0 (0%)	0 (0%)	5 (5.2%)	0 (0%)
Peru	7 (4.4%)	0 (0%)	5 (14%)	2 (2.1%)	0 (0%)
Philippines	7 (4.4%)	4 (24%)	2 (5.4%)	1 (1.0%)	0 (0%)
Qatar	1 (0.6%)	0 (0%)	0 (0%)	1 (1.0%)	0 (0%)
Singapore	17 (11%)	3 (18%)	4 (11%)	10 (10%)	0 (0%)
Sri Lanka	15 (9.4%)	0 (0%)	6 (16%)	9 (9.3%)	0 (0%)
Sudan	1 (0.6%)	0 (0%)	1 (2.7%)	0 (0%)	0 (0%)
Switzerland	4 (2.5%)	0 (0%)	0 (0%)	2 (2.1%)	2 (22%)
Syrian Arab Republic	1 (0.6%)	0 (0%)	0 (0%)	1 (1.0%)	0 (0%)
Thailand	1 (0.6%)	0 (0%)	1 (2.7%)	0 (0%)	0 (0%)
United Kingdom of Great Britain and Northern Ireland	5 (3.1%)	0 (0%)	1 (2.7%)	4 (4.1%)	0 (0%)
United States of America	4 (2.5%)	1 (5.9%)	2 (5.4%)	1 (1.0%)	0 (0%)
Venezuela, Bolivarian Republic of...	1 (0.6%)	0 (0%)	0 (0%)	1 (1.0%)	0 (0%)
Viet Nam	20 (13%)	4 (24%)	6 (16%)	9 (9.3%)	1 (11%)

Experience of dengue					
Hospitalisation for dengue management	32 (55%)	15 (88%)	16 (43%)		1 (25%)
Intensive Care Unit (ICU) Treatment	6 (10%)	2 (12%)	4 (11%)		0 (0%)
Outpatient management for uncomplicated dengue	20 (34%)	0 (0%)	17 (46%)		3 (75%)
Age of family member					
0-5	1 (3.4%)	0 (0%)	1 (5.0%)		0 (0%)
5-17	7 (24%)	2 (40%)	5 (25%)		0 (0%)
18-29	5 (17%)	1 (20%)	3 (15%)		1 (25%)
30-39	4 (14%)	0 (0%)	3 (15%)		1 (25%)
40-49	4 (14%)	1 (20%)	1 (5.0%)		2 (50%)
50-59	6 (21%)	1 (20%)	5 (25%)		0 (0%)
60-69	2 (6.9%)	0 (0%)	2 (10%)		0 (0%)
Research focus					
Basic science	9 (5.6%)	0 (0%)	3 (8.1%)	6 (6.2%)	0 (0%)
Clinical research	98 (61%)	0 (0%)	23 (62%)	72 (74%)	3 (33%)
Epidemiology and Public health	22 (14%)	0 (0%)	7 (19%)	11 (11%)	4 (44%)
Other	6	0 (0%)	0 (0%)	5	1
Clinical specialization					
In primary care / family medicine	15 (9.4%)		5 (14%)	8 (8.2%)	2 (22%)
Secondary care / specialty medicine - Infectious diseases	28 (17,5%)		6 (16,2%)	22 (22,7%)	0 (0%)
Secondary care / specialty medicine (Internal medicine)	7 (4,37)		2 (5,4%)	5 (5,15%)	0 (0%)
Secondary care / specialty medicine - Paediatric Medicine	4 (2,5%)		1 (2.7%)	3 (3%)	0 (0%)

Secondary care / specialty medicine (Critical care)	13 (8%)		1 (2.7%)	12 (12,4%)	0 (0%)
Secondary care / specialty medicine (not specified)	9 (5.6%)		2 (5.4%)	7 (7.2%)	0 (0%)
Secondary care / specialty medicine (other)	18 (11,25%)		6 (16,2%)	12 (12,4%)	0 (0%)

1.2 Table Ib-4 Results of the first Delphi round

Outcome measure	People with lived experience					Healthcare professionals / researchers with lived experience					Healthcare professionals / researchers without lived experience					Representatives of other dengue stakeholders*				
	N	Not rated	% 1-3	% 4-6	% 7-9	N	Not rated	% 1-3	% 4-6	% 7-9	N	Not rated	% 1-3	% 4-6	% 7-9	N	Not rated	% 1-3	% 4-6	% 7-9
Development of shock	48	6	7%	5%	88%	64	1	2%	5%	94%	162	1	2%	5%	93%	17	1	0%	0%	100%
Fatigue	48	0	2%	29%	69%	64	0	27%	42%	31%	162	1	14%	48%	38%	17	1	12%	50%	38%
Fever	48	0	2%	25%	73%	64	1	8%	49%	43%	162	0	8%	43%	49%	17	0	12%	35%	53%
Health Related Quality of Life	48	1	9%	21%	70%	64	1	6%	41%	52%	162	1	4%	39%	57%	17	1	6%	44%	50%
Mortality/Survival	48	0	4%	6%	90%	64	1	0%	10%	90%	162	2	2%	8%	90%	17	0	0%	18%	82%
Organ failure	48	3	11%	4%	84%	64	0	0%	11%	89%	162	2	2%	6%	92%	17	1	6%	12%	81%
Pain	48	1	0%	30%	70%	64	0	12%	53%	34%	162	1	14%	40%	45%	17	0	29%	47%	24%
Plasma viraemia/Viral load	48	10	8%	18%	74%	64	1	8%	51%	41%	162	3	9%	38%	52%	17	1	12%	38%	50%
Platelet count	48	3	2%	9%	89%	64	0	6%	34%	59%	162	1	4%	30%	66%	17	0	0%	35%	65%
Recovery	48	2	0%	17%	83%	64	0	8%	33%	59%	162	0	3%	22%	75%	17	1	12%	6%	81%

Require care at the hospital and/or in the ICU/ITU	48	3	0%	13%	87%	64	0	5%	11%	84%	162	1	1%	9%	91%	17	0	0%	18%	82%
Severe bleeding	48	1	11%	2%	87%	64	0	3%	11%	86%	162	1	2%	6%	92%	17	0	0%	0%	100%
Severe fluid leakage	48	2	7%	20%	74%	64	2	2%	6%	92%	162	3	3%	6%	91%	17	2	0%	7%	93%
Severe gastrointestinal symptoms	48	1	11%	19%	70%	64	0	3%	36%	61%	162	2	3%	29%	68%	17	1	6%	19%	75%

*Responses from this group were used to inform outcome selection and discussions but were not included in the analysis.

1.3 Table Ib-5 Summary of the most popular suggested outcomes after Delphi round 1 and provided feedback for participants in round 2 with reasons for exclusion.

Suggested outcome	Reason for exclusion
"Biomarkers" (such as electrolytes, ferritin, etc)	It was agreed that while other biological markers are very important and can provide indirect evidence of treatment response, they will not be discussed in this Delphi process. The variety of biological markers is extensive, and although some are used in clinical practice, they are usually not suitable as primary outcomes for intervention effectiveness trials.
Adverse events/effects	Adverse events, treatment-emergent adverse events, and serious adverse events are mandatory assessments in any intervention study by default. Therefore, there is no need to include this outcome in this Delphi consensus process.
Length of hospital stay	After thorough discussion involving the management group and steering committee members, it was agreed that hospital stay duration policies vary significantly across different geographical regions and settings. As such, this outcome may often reflect healthcare policy differences and not necessarily be associated with the treatment efficacy.

Need for blood transfusion/Fluid replacement	These outcomes reflect clinical events that occur during patient care and/or serve as an indirect sign of severity. However, treatment guidelines may substantially vary from country to country, making these outcomes challenging to measure and thus less suitable for inclusion.
Long term outcomes/chronic sequelae post-acute illness	Measuring sequelae is often considered not feasible in clinical trials of dengue treatments. However, emerging evidence suggests that sequelae of infectious diseases is an understudied problem that may pose a significant burden to public and global health. More in-depth investigation is critically needed. There was a consensus among management group and steering committee members that harmonisation in the assessment of sequelae is needed, and further research should be conducted in this field, but it has been decided at the start of DEN-CORE project that the process will focus on acute phase Dengue only, leaving sequelae for future endeavours.
Specific pain in the different body parts (e.g. headache, abdominal, etc.)	This outcome is already encompassed within the broader category of "pain" outcome.
Time to recovery	Outcome “recovery” has been refined and included under the term "time to recovery." Specific methods/measurement instruments for measuring this outcome will be determined later.
NS1 Antigen	This has been incorporated as part of the "Viral Load" outcome.
Dengue warning signs	These signs are generally associated with the early stages of dengue. Since hospitalised patients typically already present with warning signs, this outcome was excluded.
Evidence of plasma leakage (pleural effusion, ultrasound scan etc)	The specific approaches to the measurement and timing of plasma leakage will be decided at the second phase of the project.
Economic burden (including impact on healthcare resources, treatment costs and financial burden for patient)	This is a very important outcome which should be considered at a public health level when burden to healthcare and economy is measured. As this process is focused on determining the most critical outcomes for dengue clinical trials, economic burden will not be reviewed.

Complications (e.g. HLH, secondary infection, etc.)	Although complications are relatively rare, they are heterogeneous and some are already considered as a part of existing outcomes (e.g. shock, organ failure) while some others are usually measured as a part of adverse events and serious adverse effects assessment in clinical trials.
Neurological symptoms	According to WHO definition of “severe dengue” it is already incorporated as a part of the organ failure outcome.
Acute liver failure, renal failure, myocarditis etc	These are already included under the broader category of "Organ failure."
Ventilatory support	This is a surrogate measure of respiratory failure, which is already covered under "organ failure" and "require care in the hospital and/or ICU".
Disease literacy and education	This is a very important outcome which is of interest to be measured to evaluate interventions on a public health level. It is, however, not directly applicable to the core outcome set (COS) development for clinical trials focusing on treatment efficacy.
Duration from the onset of symptoms to the time of seeking medical attention/ Delays in healthcare	This outcome is related to patient treatment-seeking behaviour rather than being a direct outcome of the intervention.

1.4 Table Ib-6 Results following two Delphi rounds

Outcome measure	People with lived experience					Healthcare professionals / researchers with lived experience					Healthcare professionals / researchers without lived experience					Representatives of other dengue stakeholders*				
	N	Not rated	% 1-3	% 4-6	% 7-9	N	Not rated	% 1-3	% 4-6	% 7-9	N	Not rated	% 1-3	% 4-6	% 7-9	N	Not rated	% 1-3	% 4-6	% 7-9

Development of shock	17	0	0%	6%	94%	37	1	0%	3%	97%	97	0	1%	4%	95%	9	1	0%	0%	100%
Fatigue	17	0	0%	35%	65%	37	0	16%	54%	30%	97	0	12%	49%	38%	9	0	11%	44%	44%
Fever	17	0	6%	12%	82%	37	0	0%	57%	43%	97	0	9%	42%	48%	9	0	22%	56%	22%
Health Related Quality of Life	17	0	0%	18%	82%	37	2	14%	37%	49%	97	0	4%	38%	58%	9	0	11%	33%	56%
Mortality/Survival	17	1	0%	6%	94%	37	1	0%	8%	92%	97	1	0%	5%	95%	9	0	0%	11%	89%
Organ failure	17	0	0%	0%	100%	37	1	3%	3%	94%	97	1	0%	4%	96%	9	0	11%	0%	89%
Pain	17	1	0%	31%	69%	37	0	8%	51%	41%	97	0	13%	49%	37%	9	0	22%	67%	11%
Plasma viraemia/Viral load	17	0	0%	29%	71%	37	1	3%	44%	53%	97	1	5%	46%	49%	9	0	0%	56%	44%
Platelet count	17	0	0%	6%	94%	37	0	3%	24%	73%	97	0	2%	25%	73%	9	0	0%	11%	89%
Time to recovery	17	0	0%	18%	82%	37	0	3%	32%	65%	97	0	2%	19%	79%	9	1	12%	12%	75%
Require care at the hospital and/or in the ICU/ITU	17	1	0%	6%	94%	37	0	0%	5%	95%	97	0	0%	8%	92%	9	0	0%	22%	78%
Severe bleeding	17	1	0%	0%	100%	37	0	0%	8%	92%	97	0	1%	4%	95%	9	0	0%	0%	100%
Severe fluid leakage	17	0	0%	0%	100%	37	0	0%	5%	95%	97	0	2%	2%	96%	9	1	0%	12%	88%
Severe gastrointestinal symptoms	17	0	0%	12%	88%	37	0	5%	27%	68%	97	0	3%	28%	69%	9	0	11%	22%	67%

*Responses from this group were used to inform outcome selection and discussions but were not included in the analysis.

2. 'Hospitalised' dengue COS consensus meeting report

2.1 Summary

Following a two-round online Delphi survey, an online consensus meeting was held on 7 October 2024 (01:00–03:00 PM UK time) to discuss outcomes that had not reached consensus for inclusion ("in") or exclusion ("out") in the core outcome set (COS) for phase III/IV clinical trials evaluating the efficacy of treatments for people hospitalised with dengue, based on the pre-agreed definition of consensus. This report summarises the discussions held during the meeting and the resulting COS.

2.2 Pre-Meeting for people with lived experience of hospitalisation due to dengue and their family members/carers

Participants were invited to attend one of the pre-meeting sessions on the 2 October 2024 (10:00-10:30 AM UK time) or 4 October (4:00-4:30 PM UK time). These sessions were aiming to provide information on COS and what to be expected at the meeting and to offer an opportunity for people with lived experience to meet the DEN-CORE team and to ask any questions and clarify further on the COS concept and aims of the project.

2.3 "Hospitalised" COS consensus meeting participants.

A total of 48 participants from 19 countries (Table 1b-7) attended online consensus meeting, including nine non-voting members of the study team, one facilitator, and two industry representatives who participated in a non-voting capacity as observers. Additionally, 36 members of stakeholder groups attended the meeting, of whom 30 were voting participants: 25 healthcare professionals/researchers and 5 individuals with lived experience of hospitalisation due to dengue and their family members/carers.

Some participants were unable to attend the entire meeting or experienced intermittent attendance due to internet connectivity issues. As a result, the number of voting participants varied for different outcomes. The final number of votes for each outcome is recorded in this report.

In the online Delphi survey, Round 2 results were presented separately for three stakeholder groups:

a) People with lived experience of hospitalisation due to dengue and their family members/carers
b) Healthcare professionals/researchers with lived experience of dengue (including those with experience of dengue not requiring hospitalisation)
c) Healthcare professionals/researchers without lived experience of dengue

All Delphi participants were invited to express their interest in attending the online consensus meeting upon completing the survey. Those interested were informed that the meeting would be conducted in English.

Due to challenges in recruiting a sufficient number of people with lived experience, additional participants who had not taken part in the Delphi survey were invited through professional networks. Participation of these individuals in a pre-consensus meeting was mandatory in order to ensure they were familiar with the project and its' aims.

For feasibility purposes, a decision was made prior to the meeting to consolidate voting into two groups:

a) Individuals with lived experience of dengue and their family members
b) Healthcare professionals and/or researchers treating or studying dengue

This approach aligns with previous consensus meetings, such as those conducted in other COS development initiatives (1, 2).

Table Ib-7 "Hospitalised dengue" consensus meeting participants

Consensus meeting participants	N	Voting (%)
Study team members	9	0 (0%)
Facilitator	1	0 (0%)
Industry representatives	2	0 (0%)
Healthcare professionals and/or researchers treating/studying dengue	31	25(81%)
Individuals with lived experience of dengue and their family members	5	5 (100%)
Total	**48**	**30**

Country of residence of "Hospitalised dengue" consensus meeting participants.				
Country of residence	**Study team members**	**Industry representatives**	**Healthcare professionals and/or researchers treating/studying dengue**	**Individuals with lived experience of dengue and their family members**
Australia			1	
Brazil			1	1
Bolivia			1	
Colombia			4	
Cyprus	1			
India			1	
Indonesia			2	
Malaysia			4	1
Nepal			1	
Pakistan			1	
Philippines				1
Peru			1	
Russia	4			

Switzerland		2		
Singapore			2	
Sri Lanka			3	1
United Kingdom	2			
United States			4	
Vietnam	2		5	1
Total	9	2	31	5

2.4. Outcomes

2.4.1 Selection of outcomes for discussion

Fourteen outcomes were rated in Round 2 of the online Delphi survey. The pre-defined consensus criteria (Table Ib-1) were applied to ratings submitted by each of the three stakeholder groups:

a) People with lived experience of dengue
b) Healthcare professionals/researchers with lived experience of dengue
c) Healthcare professionals/researchers without lived experience of dengue

As a result of the Delphi survey, seven outcomes met the pre-specified criteria for *"consensus in"* and were included in the core outcome set (COS). No outcomes met the criteria for *"consensus out"*. Seven outcomes that did not reach consensus were selected for discussion at the consensus meeting.

Before the discussion, outcomes that had already reached consensus in Round 2 were presented to meeting participants (Table 1b-6). Outcomes selected for discussion were introduced alongside those from the same domain that had already been included in the COS. Participants were then invited to share their perspectives on the relevance and value of each outcome for the COS.

Following the discussions, participants anonymously rated each outcome using a 1–9 Likert scale (1 = *not that important*, 9 = *critically important*). An option to select *"unable to rate"* was provided for those who did not feel qualified to assess a particular outcome.

Voting was conducted via Zoom's online polling feature and facilitated by the study team. The discussion and rating process was led by an experienced independent facilitator.

2.4.2 Life impact outcomes

Health related quality of life

During the discussion on "health-related quality of life (HRQoL)", participants emphasised its importance, particularly in the context of long-term health outcomes. However, it was clarified that the current process focuses solely on the acute phase. Unlike "*time to recovery"*, which includes both hospitalisation and post-hospitalisation outcomes, HRQoL is considered only within acute care in this process.

A question was raised regarding regulatory acceptance of HRQoL assessments in clinical trials for hospitalised patients, as regulators generally recognise QoL measures in chronic or community-based studies rather than in acute-phase conditions.

Additionally, challenges in standardising HRQoL assessments across cultures were highlighted due to their subjective nature. However, it was noted that decisions on specific measurement tools would be addressed later in the process, during the *how to measure* stage, if the outcome is included in the core set.

Outcome discussion and rating:

Health-related quality of life	Unable to rate	% rating 1-3	% rating 4-6	% rating 7-9
Healthcare professionals and/or researchers treating/studying dengue	-	5/24 (21%)	11/24(46%)	8/24 (33%)
Individuals with lived experience of dengue and their family members	-	-	4/4 (100%)	-
Result	**Outcome not included in COS for "hospitalised dengue"**			

2.4.3 Physiological/clinical outcomes

Time to recovery

Given the significant burden of dengue in many countries and its strain on hospital resources, reducing hospital stay duration was suggested as a key metric of interest. However, concerns were raised about the feasibility of measuring "time to recovery" in every trial and whether it is essential for all studies. Additionally, it was noted that such assessments would require evaluations at later time points, which could add complexity to study designs.

Outcome discussion and rating:

Time to recovery	Unable to rate	% rating 1-3	% rating 4-6	% rating 7-9
Healthcare professionals and/or researchers treating/studying dengue	-	3/25 (12%)	6/25 (24%)	16/25(64%)
Individuals with lived experience of dengue and their family members	-	-	2/5 (40%)	3/5 (60%)
Result	**Outcome not included in COS for "hospitalised dengue"**			

Severe gastrointestinal symptoms

Concerns were raised about the need for a clear definition of "severe gastrointestinal symptoms", as abdominal pain could be linked to the acute onset of plasma leakage, which is already included as an outcome.

While severe gastrointestinal symptoms were recognised as important, it was noted that including them as a core outcome in every study may not be feasible. However, it was reiterated that exclusion from the core outcome set (COS) does not diminish their significance but rather indicates that they may not be necessary for all trials.

Outcome discussion and rating:

Severe gastrointestinal symptoms	Unable to rate	% rating 1-3	% rating 4-6	% rating 7-9
Healthcare professionals and/or researchers treating/studying dengue	1	5/24 (21%)	10/24(42%)	9/24 (37%)
Individuals with lived experience of dengue and their family members	-	-	3/5 (60%)	2/5 (40%)
Result	**Outcome not included in COS for "hospitalised dengue"**			

Pain

"Pain" was considered a straightforward outcome to measure, with the possibility of daily updates during the acute phase. It was highlighted that proper assessment would require recording NSAID use, including the type and timing of administration. If integrated into a scoring system alongside fever, daily pain measurement could be a useful outcome.

Previous research assessing pain using a visual analogue scale administered by nursing staff did not find an association with dengue haemorrhagic fever (DHF) or severe dengue, leading to scepticism about its value as an outcome. It was argued that even if pain is not linked to severity through other measures, it could still be valuable as an independent outcome.

While aches and pains are common among dengue patients, some suggested that right hypochondrial pain might be more significant. Concerns were also raised about pain subjective nature, as it may result from both the disease itself and hospital procedures. Some participants felt that pain should not be included in the core outcome set, as other outcomes are more critical.

A person with lived experience highlighted that while dengue-related pain can be severe and debilitating, it is often self-limited. Additionally, many individuals with lived experience reported that fatigue was a more prominent and impactful symptom than pain, suggesting that fatigue might be a higher priority for measurement in every study.

Outcome discussion and rating:

Pain	Unable to rate	% rating 1-3	% rating 4-6	% rating 7-9
Healthcare professionals and/or researchers treating/studying dengue	-	9/24 (37%)	12/24(50%)	3/24 (13%)
Individuals with lived experience of dengue and their family members	-	1/3 (33%)	2/3 (67%)	-
Result	**Outcome not included in COS for "hospitalised dengue"**			

Fever

Opinions on fever as an outcome were divided. Some participants did not prioritise fever, like their stance on pain, while others supported its inclusion due to its association with viremia, NS1 levels, and vascular leakage. Since fever is easily measurable and quantifiable, it was considered relevant, particularly in studies testing direct antiviral agents.

Fever was noted to be especially critical in cases of co-infection and could provide useful insights at the onset of the vascular leakage phase. However, some argued that if they were receiving treatment for dengue, they would expect a life-saving intervention rather than one that only alleviates symptoms like fever.

Concerns were raised about whether fever should be included as a core outcome in all trials, as its relevance depends on the study context. For example, fever resolution is important for trials on antipyretics or antivirals but may not be meaningful in studies focused on IV fluids or transfusions.

It was also noted that fever traditionally plays a role in clinical trials and is less subjective than pain. Fever resolution can help temporally align patient analysis during the critical phase. However, since most cases of dengue shock and severe dengue occur after fever subsides, its significance differs from that of other infections. Some supported measuring fever but were uncertain whether it should be considered a core outcome.

Outcome discussion and rating:

Fever	**Unable to rate**	**% rating 1-3**	**% rating 4-6**	**% rating 7-9**
Healthcare professionals and/or researchers treating/studying dengue	-	9/24 (37%)	5/24 (21%)	10/24(42%)
Individuals with lived experience of dengue and their family members	-	1/4 (25%)	2/4 (50%)	1/4 (25%)
Result	**Outcome not included in COS for "hospitalised dengue"**			

Fatigue

There was a comment that measuring time to recovery may better capture fatigue rather than assessing fatigue in isolation. Some participants noted that fatigue is highly non-specific and subjective, making it a less reliable outcome.

Additionally, fatigue was reported by only a few patients and was not considered particularly significant, as it tends to be short-lived. It was also noted that while lethargy is a recognised warning sign in dengue, fatigue itself is not.

Outcome discussion and rating:

Fatigue	**Unable to rate**	**% rating 1-3**	**% rating 4-6**	**% rating 7-9**

Healthcare professionals and/or researchers treating/studying dengue	-	10/25(40%)	10/25(40%)	5/25 (20%)
Individuals with lived experience of dengue and their family members	-	1/4 (25%)	2/4 (50%)	1/4 (25%)
Result	**Outcome not included in COS for "hospitalised dengue"**			

Viral load

Viremia was considered an important measure, particularly for antiviral therapies. However, its variability over time and across serotypes makes proper timing crucial for accurate assessment.

Concerns were raised about requiring viral load measurement in all studies, as many institutions lack the necessary resources and infrastructure. It was suggested that plasma viremia could be a useful outcome in Phase 2 trials, but Phase 3 studies should focus on clinical endpoints instead.

From a patient perspective, viral load measurement was not seen as a priority, and some researchers also favored clinical endpoints over virological ones. Additionally, it was noted that measuring viral load is resource-intensive and may not be feasible for many treatment facilities.

Despite these challenges, viral load was considered valuable for clinical trials beyond antivirals, including those evaluating immunomodulatory therapies, where it may help assess whether treatments prolong viremia. It was also emphasised that understanding viremia remains critical for improving clinical outcomes, as assumptions about treatment effectiveness need to be supported by such measurements.

Viral load	**Unable to rate**	**% rating 1-3**	**% rating 4-6**	**% rating 7-9**
Healthcare professionals and/or researchers treating/studying dengue	-	3/25 (12%)	7/25 (28%)	15/25(60%)
Individuals with lived experience of dengue and their family members	1	-	2/3 (67%)	1/3 (33%)
Result	**Outcome not included in COS for "hospitalised dengue"**			

2.5 Results of the "hospitalised" dengue COS consensus meeting

Seven outcomes were included in the core outcome set after the two round online Delphi survey. No additional outcomes were added as a result of consensus meeting.

Table Ib-8 Outcomes voted during "hospitalised" consensus meeting

Outcome	People with lived experience of dengue and their family members				Healthcare professionals and/or researchers treating/studying dengue				Result
	Unable to rate	1-3	4-6	7-9	Unable to rate	1-3	4-6	7-9	
Health Related Quality of Life	-	-	4/4 (100 %)	-	-	5/24 (21%)	11/24 (46%)	8/24 (33%)	Excluded
Time to recovery	-	-	2/5 (40%)	3/5 (60%)	-	3/25 (12%)	6/25 (24%)	16/25 (64%)	Excluded
Severe gastrointestinal symptoms	-	-	3/5 (60%)	2/5 (40%)	1	5/24 (21%)	10/24 (42%)	9/24 (37%)	Excluded
Pain	-	1/3 (33%)	2/3 (67%)	-	-	9/24 (37%)	12/24 (50%)	3/24 (13%)	Excluded
Fever	-	1/4 (25%)	2/4 (50%)	1/4 (25%)	-	9/24 (37%)	5/24 (21%)	10/24 (42%)	Excluded
Fatigue	-	1/4 (25%)	2/4 (50%)	1/4 (25%)	-	10/25 (40%)	10/25 (40%)	5/25 (20%)	Excluded
Plasma viremia/viral load	1	-	2/3 (67%)	1/3 (33%)	-	3/25 (12%)	7/25 (28%)	15/25 (60%)	Excluded

Table Ib-9 Outcomes included in 'hospitalised' dengue COS

Domain	Outcome	Outcome description (from the Delphi survey)
Mortality/ survival	Mortality/survival	Survival beyond acute dengue illness
Physiological /clinical	Development of shock	Shock is a severe medical emergency where the body's circulatory system fails to provide sufficient blood flow, resulting in not enough oxygen being delivered to the cells. This can occur for a variety of reasons, but in dengue this usually results from increased permeability of blood vessels, resulting in leakage of plasma out of the vessels. Shock can be recognized by at least two of the following signs: signs of poor blood flow (hypoperfusion), skin that is cold and clammy, and a rapid but weak pulse; confusion or changes in how alert someone is (altered mental status); pulse pressure (the difference between the systolic and diastolic blood

		pressure readings) that is narrow (20mmHg or less); low blood pressure for the person's age; and a fast heart rate (over 100 beats per minute). Each of these symptoms points to the body's struggle to maintain blood flow and oxygen supply to vital organs, highlighting the need for urgent medical intervention.
	Organ failure	Organ failure is a critical medical condition where one or more of the body's vital organs stop working correctly. This can involve major organs like the heart, liver, kidneys, or lungs or CNS (impaired consciousness leading to severe, life-threatening complications. For instance, severe heart failure significantly limits how much physical activity a person can do, while respiratory failure may make it hard to breath and require the use of additional oxygen or assisted ventilation. Kidney failure could mean needing regular dialysis (a treatment to remove waste from the blood when the kidneys can't). The onset of organ failure indicates a serious decline in health, requiring immediate medical attention to support the organs and prevent life threatening complications.
	Severe bleeding	This refers to bleeding or haemorrhage that requires medical intervention. Defined as bleeding resulting in haemodynamic compromise or bleeding that necessitates an intervention, for example a transfusion (donated blood is given to the affected person to replace what they have lost).
	Severe fluid leakage	Severe leakage leading to fluid accumulation refers to the excessive buildup of fluid in different parts of the body, leading to conditions such as peripheral edema (swelling of the lower limbs due to fluid retention), pleural effusion (fluid around the lungs), ascites (fluid in the abdomen), or pericardial effusion (fluid around the heart). These conditions can be identified through physical exams, imaging techniques like X-rays or ultrasound, indicating a significant accumulation of fluid. Importantly, this outcome highlights the presence of severe fluid buildup without it necessarily causing respiratory distress (difficulty breathing) or hemodynamic compromise (problems with blood flow).
	Platelet count	Refers to measuring the number of platelets in a person's blood. Platelets are cells that help our blood clot to stop bleeding. A normal platelet count is important as it helps prevent excessive bleeding or clotting. The count is measured by a blood test and is expressed as the number of platelets per volume of blood. A low platelet count is commonly seen in dengue,

		known as thrombocytopenia and can increase the risk of bleeding and bruising.
Resource use	Require care at the high dependency unit and/or in the ICU/ITU	A requirement of a higher level of medical attention. This includes care in high dependancy units with wards for people who need more intensive observation, treatment and nursing care than is possible in a general ward. In more critical cases, care in an Intensive Care Unit (ICU) or Intensive Therapy Unit (ITU). The ICU/ITU is a specialised department within the hospital designed for patients with life-threatening conditions, offering continuous monitoring and support for vital organ functions (like breathing or blood pressure). This level of care is necessary when someone's health condition is severe, needing advanced treatments and close observation that only a hospital or intensive care environment can provide.

3. ‘Early stage’ COS consensus meeting report.

3.1. Summary

An online consensus meeting was held on 9 December 2024 to finalise outcomes for inclusion in the core outcome set (COS) for phase III–IV clinical trials evaluating the efficacy of treatments for people with “early stage” of the disease. The meeting followed an "adapt or adopt" approach, building on the previously agreed COS for the hospitalised stage of the disease.

To agree upon the outcomes relevant for individuals admitted to high-dependency units (HDU) or intensive care units (ICU) with dengue additional consultations were conducted with ICU and COS experts to define a suitable approach and provide recommendations for this disease stage.

This report summarises the discussions held during the “early stage” consensus meeting and recommendations made regarding outcomes to measure in individuals admitted to ICU/HDU.

3.2. Pre-meeting for people with lived experience of the disease

Only participants with experience of hospitalisation were eligible to participate in the Delphi survey. Therefore, individuals who registered to participate in the survey but reported receiving care in outpatient settings were invited to participate in the “early stage” consensus meeting. An additional call for participants was also distributed through professional networks to ensure broader inclusion.

The pre-consensus meeting took place online on 28 November 2024 (06:00-06:30 PM UK time). The aim of the meeting was to provide an overview of COS, explain what to expect during the consensus meeting, introduce the DEN-CORE team, and offer participants the opportunity to ask questions or raise concerns in advance. The session was designed to support informed and meaningful engagement from people with lived experience and their family members or carers in the development of the COS for “early stage” of the disease.

3.3 “Early stage” consensus meeting participants

A total of 30 participants from 12 countries (Table Ib-10) attended online consensus meeting. From these 20 were voting participants (15 healthcare professionals/researchers treating/studying dengue, 3 healthcare professionals/researchers with lived experience of dengue, 2 people with lived experience of dengue or their family members or carers), 10 non-voting participants (7 members of the study team and 3 non-voting industry representatives).

Given the small number of participants with lived experience, a decision was made to consolidate all voting participants into a single group for the purpose of consensus decisions.

Table Ib-10. "Early stage" consensus meeting participants

Consensus meeting participants	N	Voting (%)
Study team members	7	0 (0%)
Industry representatives	3	0 (0%)
Healthcare professionals and/or researchers treating/studying dengue	15	20 (100%)
Healthcare professionals and/or researchers with lived experience of dengue	3	
Individuals with lived experience of dengue and their family members	2	
Total	30	20

Country of residence of "early stage" consensus meeting participants.					
Country of residence	Study team members	Industry representatives	Healthcare professionals/researchers treating/studying dengue	Healthcare professionals/researchers with lived experience of dengue	People with lived experience of dengue and their family members
Brazil			2		
China		1			
Colombia			3	1	1
Cyprus	1				
Malaysia			1		
Nepal			2		
Russia	3				
Switzerland		2			
Sri Lanka			1		
UK	2		1		
USA			2	1	
Viet Nam	1		3	1	1
Total	7	3	15	3	2

3.4 Outcomes

3.4.1 Selection of outcomes for "early stage" consensus meeting

An *adapt or adopt* approach was used during the meeting. Outcomes considered critical for inclusion in the "hospitalised" dengue COS were also deemed applicable to the "early stage".

Outcomes that were not selected for inclusion in the hospitalised dengue COS were revised and discussed for their potential relevance to "early stage" dengue COS.

In line with an a priori decision made by the core group, "need for hospitalisation" was included as a standalone outcome for "early stage" of the disease, reflecting its importance as a resource use indicator. No objections to this approach were raised by meeting participants.

3.4.2 Physiological/clinical domain

Time to recovery

Definition: *Time to recovery refers to the period beyond the acute phase of dengue, during which an individual regains health and well-being following infection. This outcome encompasses not only the disappearance of physical symptoms and the return to normal physiological functioning, but also the resumption of everyday activities and the psychological and emotional adjustment after illness—leading to either a return to pre-illness health or adaptation to a new normal.*

Although the focus of this project was only on acute phase, "time to recovery" was included in the Delphi process to explore whether it could be measured in a simplified way following dengue infection. The outcome was not prioritised neither in Delphi nor in "hospitalised" consensus meeting. One key challenge identified was the feasibility of measuring long-term recovery in clinical trial setting. As a result, a separate COS for post-dengue recovery was suggested to comprehensively assess longer-term impacts of the disease. Given these considerations, the decision was made not to vote on this outcome for inclusion in the "early stage" COS.

Resolution of acute symptoms

In Delphi survey and in "hospitalised" consensus meeting outcomes "pain," "fever," "fatigue," and "severe gastrointestinal symptoms" were rated as separate outcomes. None of these individual outcomes met the predefined thresholds for inclusion in "hospitalised" dengue COS.

Prior to the "early stage" consensus meeting a decision was made by the management group to combine these individual outcomes into a combined outcome: "resolution of acute symptoms." This composite outcome was discussed extensively during the meeting. While participants acknowledged its clinical relevance—particularly for early stage —many expressed concerns about its limited utility in assessing disease severity. It was noted that symptom resolution does not necessarily indicate improved clinical status, as patients can still deteriorate or progress to severe dengue even as some symptoms resolve. As such, several participants felt that including it in the COS for the early stage would not add meaningful value and could be misleading.

However, people with lived experience of dengue strongly emphasised the importance of symptom burden and symptom relief. Time to resolution of fever was considered especially important from the patient perspective. While pain and fatigue were also seen as significant from a patient standpoint, concerns were raised regarding their subjective nature and the difficulty in standardising their measurement. Fatigue, in particular, was suggested for exclusion due to these challenges.

Some participants recommended using daily symptom scores, as done in early-stage influenza trials, to capture meaningful changes over time—even if based on subjective reporting.

<u>Outcome discussion and rating:</u>

Resolution of acute symptoms	Unable to rate	% rating 1-3	% rating 4-6	% rating 7-9
All stakeholders	-	-	3/20 (15%)	17/20(85%)
Result	Outcome included in COS for “early-disease dengue”			

Plasma viremia/viral load

The inclusion of viral load as an outcome was discussed primarily in the context of trials, where antiviral therapies are likely to be evaluated. Several participants highlighted the importance of viral load as a direct and objective measure of antiviral effect, particularly during the viraemic phase. It was emphasized that including viral load would help standardise assessments across trials and enhance comparability of findings.

There was consensus that measuring the rate of viral decline could serve as a critical indicator of treatment efficacy. Viral load was also seen as particularly relevant for distinguishing primary from secondary endpoints, especially when evaluating early therapeutic interventions.

However, feasibility concerns were raised, particularly for trials conducted in low-resource settings where routine viral load testing may not be available. Despite this, the overall view supported the inclusion of viral load, recognizing its value in providing robust and objective evidence on the biological impact of antiviral agents.

Outcome discussion and rating:

Viral load	Unable to rate	% rating 1-3	% rating 4-6	% rating 7-9
All stakeholders	-	-	3/20 (15%)	17/20(85%)
Result	Outcome included in COS for “early-disease dengue”			

3.4.3 Life impact domain

Health-related Quality of Life

There was broad support for including HRQoL as an outcome. Multiple participants emphasized its relevance in capturing the broader impact of dengue beyond immediate clinical symptoms. HRQoL was seen as a valuable measure for understanding the patient experience during acute illness.

However, some concerns were raised regarding the timing and scope of HRQoL assessment. It was noted that short-term evaluation (e.g. at day 7) may fail to capture issues such as brain fog or prolonged fatigue, which can be more incapacitating than acute symptoms. In this context, a comparison was drawn with the exclusion of “time to recovery” from the voting list—suggesting that while both outcomes are important, they require careful definition and timing of assessment.

Participants suggested that HRQoL should be specifically defined in relation to the acute phase of illness. Despite the need for clarity around measurement timing, there was agreement that HRQoL is a distinct and meaningful outcome that warrants inclusion.

Outcome discussion and rating:

Health-related Quality of life	Unable to rate	% rating 1-3	% rating 4-6	% rating 7-9
All stakeholders	-	-	3/19 (16%)	16/19(84%)
Result	Outcome included in COS for "early-disease dengue"			

3.5 Results of the "early stage" consensus meeting

Seven outcomes were included in the COS set after the two round online Delphi survey for "hospitalised" dengue COS (Table Ib-6). These outcomes were formally ratified for inclusion in "early stage" COS.

Outcome "Need for hospitalisation" was added as a resource use outcome upon discussion with the management group. Three additional outcomes were added in "early stage" dengue COS as a results of consensus meeting (Table Ib-11).

Table Ib-11. Outcomes voted during "early stage" consensus meeting

Outcome	All stakeholders				Result
	Unable to rate	1-3	4-6	7-9	
Health-related Quality of life	-	-	3/19 (16%)	16/19 (84%)	Outcome included in the COS for "early-stage" dengue
Resolution of acute symptoms	-	-	3/20 (15%)	17/20 (85%)	Outcome included in the COS for "early-stage" dengue
Plasma viremia/viral load	-	-	3/20 (15%)	17/20 (85%)	Outcome included in the COS for "early-stage" dengue

Table Ib-12 Outcomes included in "early stage" COS

Domain	Outcome	Outcome description (from the Delphi survey)
Mortality/ survival	Mortality/ survival	Survival beyond acute dengue illness

Physiological /clinical	Development of shock	Shock is a severe medical emergency where the body's circulatory system fails to provide sufficient blood flow, resulting in not enough oxygen being delivered to the cells. This can occur for a variety of reasons, but in dengue this usually results from increased permeability of blood vessels, resulting in leakage of plasma out of the vessels. Shock can be recognized by at least two of the following signs: signs of poor blood flow (hypoperfusion), skin that is cold and clammy, and a rapid but weak pulse; confusion or changes in how alert someone is (altered mental status); pulse pressure (the difference between the systolic and diastolic blood pressure readings) that is narrow (20mmHg or less); low blood pressure for the person's age; and a fast heart rate (over 100 beats per minute). Each of these symptoms points to the body's struggle to maintain blood flow and oxygen supply to vital organs, highlighting the need for urgent medical intervention.
	Organ failure	Organ failure is a critical medical condition where one or more of the body's vital organs stop working correctly. This can involve major organs like the heart, liver, kidneys, or lungs or CNS (impaired consciousness leading to severe, life-threatening complications. For instance, severe heart failure significantly limits how much physical activity a person can do, while respiratory failure may make it hard to breath and require the use of additional oxygen or assisted ventilation. Kidney failure could mean needing regular dialysis (a treatment to remove waste from the blood when the kidneys can't). The onset of organ failure indicates a serious decline in health, requiring immediate medical attention to support the organs and prevent life threatening complications.
	Severe bleeding	This refers to bleeding or haemorrhage that requires medical intervention. Defined as bleeding resulting in haemodynamic compromise or bleeding that necessitates an intervention, for example a transfusion (donated blood is given to the affected person to replace what they have lost).
	Severe fluid leakage	Severe leakage leading to fluid accumulation refers to the excessive buildup of fluid in different parts of the body, leading to conditions such as peripheral edema (swelling of the lower limbs due to fluid retention), pleural effusion (fluid around the lungs), ascites (fluid in the abdomen), or pericardial effusion (fluid around the heart). These conditions can be identified through physical exams, imaging techniques like X-rays or ultrasound, indicating a significant accumulation of fluid. Importantly, this outcome highlights the presence of severe fluid buildup without it necessarily causing respiratory distress

		(difficulty breathing) or hemodynamic compromise (problems with blood flow).
	Resolution of acute symptoms	The resolution of acute symptoms refers to the stage where the initial, uncomfortable symptoms of the illness start to disappear. This typically includes a decline in high fever, reduction in headache intensity, easing of pain behind the eyes, alleviation of joint and muscle pain, and a decrease in fatigue and skin rash.
Biomarkers	Platelet count	Refers to measuring the number of platelets in a person's blood. Platelets are cells that help our blood clot to stop bleeding. A normal platelet count is important as it helps prevent excessive bleeding or clotting. The count is measured by a blood test and is expressed as the number of platelets per volume of blood. A low platelet count is commonly seen in dengue, known as thrombocytopenia and can increase the risk of bleeding and bruising.
	Plasma viremia/viral load	The amount of virus present in the blood plasma of an individual. When someone is infected with a virus, that virus can multiply inside their body. The viral load measurement tells doctors how many virus particles are circulating in the blood.
Life impact	Health-related Quality of life	This is a broad concept that reflects how a person views the impact of acute dengue illness and its management on their life. It encompasses several key areas: physical well-being, mental and emotional health, and social connections. Specifically in the context of acute dengue illness, Health-related QoL is about understanding how a person feels about their ability to perform daily activities, maintain physical health, manage the emotional stresses brought on by the illness, and engage in meaningful social interactions.
Resource use	Need for hospitalisation	A requirement of a higher level of medical attention that cannot be adequately provided at home or in a basic healthcare setting. This includes care in a hospital, where specialised medical staff and equipment are available around the clock

	Require care at the high dependency unit and/or in the ICU/ITU	A requirement of a higher level of medical attention. This includes care in high dependancy units with wards for people who need more intensive observation, treatment and nursing care than is possible in a general ward. In more critical cases, care in an Intensive Care Unit (ICU) or Intensive Therapy Unit (ITU). The ICU/ITU is a specialised department within the hospital designed for patients with life-threatening conditions, offering continuous monitoring and support for vital organ functions (like breathing or blood pressure). This level of care is necessary when someone's health condition is severe, needing advanced treatments and close observation that only a hospital or intensive care environment can provide.

4. Table Ib-13 Delphi process and Consensus meeting results

Outcome	Description (as presented to the Delphi participants)	"Hospitalised" stage COS					"Early stage" COS	Results
		%Stakeholders voting 7-9 in R2 online Delphi			%Stakeholders voting 7-9 in 'hospitalised' consensus meeting		%Stakeholders voting 7-9 in consensus meeting	
		P*	HCP / RS** with lived experience	HCP / RS without lived experience	P	HCP/ RS		
Mortality/survival	Survival beyond acute dengue illness	94%	92%	95%	NA	NA	NA	Outcome included in the COS both for **"hospitalised" and "early-stage"** dengue.
Health Related Quality of Life	This is a broad concept that reflects how a person views the impact of acute dengue illness and its management on their life. It encompasses several key areas: physical well-being, mental and emotional health, and social connections. Specifically in the	82%	49%	58%	-	33%	84%	Outcome excluded for the "hospitalised" dengue COS following consensus meeting. Outcome included in the COS for **"early-stage"**

		context of acute dengue illness, Health-related QoL is about understanding how a person feels about their ability to perform daily activities, maintain physical health, manage the emotional stresses brought on by the illness, and engage in meaningful social interactions.							
Time to recovery		Recovery refers to the period during which a person regains their health and well-being after experiencing an illness or medical treatment. This process includes disappearance of symptoms, the body's return to its regular functioning, and the ability to engage in everyday tasks and activities. Recovery encompasses not only the physical healing but also the mental and emotional adjustment to life after the illness, leading back to a normal or a new normal state.	82%	65%	79%	60%	64%	NA	Outcome **not included** in the COS
Resolution of acute symptoms	Fatigue	New onset or worsening in severity or duration of feeling exhausted, having too little energy, or needing more rest during acute dengue illness	65%	30%	38%	25%	20%	85%	Individual outcomes were excluded for the "hospitalised" dengue COS following consensus meeting. Outcome "Resolution of acute symptoms" included in the COS for **"early-stage"** dengue.
	Fever	New onset or worsening of problems related to the body temperature (e.g. fever that comes and goes, chills or shivers, feeling too cold or too hot).	82%	43%	48%	25%	42%		
	Pain	New or worsening feelings of hurt including aches, stinging, throbbing, or burning that could be sharp or dull, and constant or	69%	41%	37%	-	13%		

		variable. (e.g headache, muscle pain, joint pain, abdominal pain, etc)							
	Severe gastrointestinal symptoms	New onset or the worsening of problems related to the gastrointestinal tract, which includes the stomach and intestines. These symptoms can include persistent nausea (feeling like you need to vomit), vomiting more than twice a day, or ongoing diarrhoea (loose, watery stools), and abdominal tenderness.	88%	68%	69%	40%	37%		
Progression to severe disease	Organ failure	Organ failure is a critical medical condition where one or more of the body's vital organs stop working correctly. This can involve major organs like the heart, liver, kidneys, or lungs or CNS (impaired consciousness leading to severe, life-threatening complications. For instance, severe heart failure significantly limits how much physical activity a person can do, while respiratory failure may make it hard to breath and require the use of additional oxygen or assisted ventilation. Kidney failure could mean needing regular dialysis (a treatment to remove waste from the blood when the kidneys can't). The onset of organ failure indicates a serious decline in health, requiring immediate medical attention to support the organs and prevent life threatening complications.	100%	94%	96%	NA	NA	NA	Outcomes included in the COS following Delphi survey both for **"hospitalised" and "early-stage"** dengue.
	Severe fluid leakage	Severe leakage leading to fluid accumulation refers to the excessive buildup of fluid in different parts of the body, leading to	100%	95%	96%	NA	NA	NA	

		conditions such as peripheral edema (swelling of the lower limbs due to fluid retention), pleural effusion (fluid around the lungs), ascites (fluid in the abdomen), or pericardial effusion (fluid around the heart). These conditions can be identified through physical exams, imaging techniques like X-rays or ultrasound, indicating a significant accumulation of fluid. Importantly, this outcome highlights the presence of severe fluid buildup without it necessarily causing respiratory distress (difficulty breathing) or hemodynamic compromise (problems with blood flow).							
	Development of shock	Shock is a severe medical emergency where the body's circulatory system fails to provide sufficient blood flow, resulting in not enough oxygen being delivered to the cells. This can occur for a variety of reasons, but in dengue this usually results from increased permeability of blood vessels, resulting in leakage of plasma out of the vessels. Shock can be recognised by at least two of the following signs: signs of poor blood flow (hypoperfusion), skin that is cold and clammy, and a rapid but weak pulse; confusion or changes in how alert someone is (altered mental status); pulse pressure (the difference between the systolic and diastolic blood pressure readings) that is narrow (20mmHg or less); low blood pressure for the person's age; and a fast heart rate (over 100 beats per minute). Each of these symptoms points to the body's	94%	97%	95%	NA	NA	NA	

		struggle to maintain blood flow and oxygen supply to vital organs, highlighting the need for urgent medical intervention.							
	Severe bleeding	This refers to bleeding or haemorrhage that requires medical intervention. Defined as bleeding resulting in haemodynamic compromise or bleeding that necessitates an intervention, for example a transfusion (donated blood is given to the affected person to replace what they have lost).	100%	92%	95%	NA	NA	NA	
	Resource use Require care at the high dependency unit and/or in the ICU/ITU	A requirement of a higher level of medical attention. This includes care in high dependency units with wards for people who need more intensive observation, treatment and nursing care than is possible in a general ward. In more critical cases, care in an Intensive Care Unit (ICU) or Intensive Therapy Unit (ITU). The ICU/ITU is a specialised department within the hospital designed for patients with life-threatening conditions, offering continuous monitoring and support for vital organ functions (like breathing or blood pressure). This level of care is necessary when someone's health condition is severe, needing advanced treatments and close observation that only a hospital or intensive care environment can provide.	94%	95%	92%	NA	NA	NA	
Need for hospitalisation			NA	NA	NA	NA	84%		Outcome "Need for hospitalisation" was added to COS for **"early stage"** prior to the consensus meeting following core team discussions.

Platelet count	Refers to measuring the number of platelets in a person's blood. Platelets are cells that help our blood clot to stop bleeding. A normal platelet count is important as it helps prevent excessive bleeding or clotting. The count is measured by a blood test and is expressed as the number of platelets per volume of blood. A low platelet count is commonly seen in dengue, known as thrombocytopenia and can increase the risk of bleeding and bruising.	94%	73%	73%	NA	NA	NA	Outcome included in the COS following Delphi survey both for **"hospitalised" and "early-stage"** dengue.
Plasma viraemia/Viral load	The amount of virus present in the blood plasma of an individual. When someone is infected with a virus, that virus can multiply inside their body. The viral load measurement tells doctors how many virus particles are circulating in the blood.	71%	53%	49%	33%	60%	85%	Outcome excluded for "hospitalised" COS. Outcome included in the COS for **"early-stage"** dengue.

5. COS for 'ICU/HDU' trials

Table Ib-14 Available Core Outcome Sets for adults and children in ICU setting.

Domain	Outcome	Adult ICU research COS (3)	Pediatric ICU Research COS (PICU COS) (4)	COS for Critical Care Ventilation Trials (5)	COS/COMS for clinical research of acute respiratory failure survivors (6, 7)	COS for trials of interventions to prevent and/or treat delirium in critically ill adults (DEL-CORS)(8)	COS for Cardiac Arrest (COSCA/P-COSCA) (9, 10)	COS for Research Evaluating Patients on Extracorporeal Membrane Oxygenation (11)
Survival/ Mortality	Survival/Mortality	■	■	■	■	■	■	■
Physiological/ Clinical	Free of life support	■						
	Delirium*	■				■		
	Pain				■			
	Pulmonary function		■		■			
	Extubation			■				
	Reintubation			■				
	Duration IMV			■				
Functioning	Cognitive function	■	■		■	■	■‡	
	Neurological function						■	■
	Muscle or nerve function				■			
	Disability							■
	Physical function		■		■		■	
	Activities of daily living						■	■
	Return to work							■
	Mental health†		■		■	■		
Resource use	Out of hospital	■						
	Length of hospital stay			■				
Life impact	Health-related QoL	■	■	■		■	■§	■
Adverse events	Adverse events							■

*In DEL-CORE suggested outcomes: delirium occurrence, severity and time to resolution, in COS for general ICU - free of delirium; †In DEL-CORE process outcome "mental health" is framed as emotional distress whicle in PICU-COS as emotional function ‡ assessed in P-COSCA process only; § in P-COSCA assesed as two separate outcomes: physical function and basic daily life skills

■instrument defined. ■ recommended instrument when no consensus ■ instrument yet not defined.

Table Ib-15 ICU and COS experts who provided feedback on recommendations regarding ICU stage

Countries of participants	Researchers	Clinicians	Both researchers and clinicians	Total N
Brazil			2	2
Canada		2		2
Germany	1			1
India			1	1
Indonesia		1		1
Malaysia		1	2	3
Nepal			1	1
Pakistan	1	2	2	5
Sri Lanka			1	1
UK		1	1	2
USA			1	1
Vietnam			2	2
Total	2	7	13	22

Table Ib-16 Level of agreement with ICU statement

Agreement with the current wording of recommendations	95%
Disagreement with the current wording of recommendations	5.00%
Agreement with the table outlining the ICU Core Outcome Sets provided alongside the recommendation	85.70%

Report of Phase II: COMS development

1. Summary

This report summarizes the Core Outcome Measurement Set (COMS) phase of the development process for dengue. Each measurement instrument report follows this structured approach:

1. *Identification of Instruments*: The outcome measurement instruments were identified in published studies, as well as research protocols related to dengue during the first phase of the process (The detailed search strategy and inclusion criteria can be found in the Appendix 1). This list was further supplemented with instruments used in other Core Outcome Set (COS) processes to ensure comprehensive coverage. The identified instruments were sent to experts in dengue research and/or clinical care for review. Three experts provided preliminary evaluations on the feasibility of each instrument. Additionally, a zoom call was held with regulatory authority representatives to find out their views on the finalised COS and outcomes included.
2. *Online Meeting*: Based on the expert reviews, an online meeting on 5 February 2025 was conducted to discuss the proposed instruments in greater detail. The feasibility of different measurement instruments and potential challenges in implementation were key topics of discussion.
3. *Preliminary Statements*: Following the online meeting, preliminary statements were developed to streamline the discussion during the hybrid meeting. These statements were circulated prior to meeting participants for review.
4. *Hybrid Consensus Meeting and final Voting*: A hybrid meeting (conducted both in person and via Zoom) was held to finalise the statements. Experts reviewed the proposed statements, made necessary refinements, and conducted a final voting process to reach consensus on the recommended measurement instruments.

2.1 "Mortality/survival" outcome measurement instrument report.

2.1.1 Identification of instruments

In the published literature and ongoing clinical trials mortality was a common outcome that was assessed at different timeframes.

Regulatory review:
Mortality is widely recognized as a robust, unbiased, and universally measurable outcome in clinical trials. Regulatory bodies favor mortality over survival as an outcome measure, as survival rates can be more challenging to interpret due to regional variations.

2.1.2 Discussion during online meeting (5 February 2025)

Post-discharge monitoring was emphasized as a critical aspect of patient care, given that some deaths occur shortly after hospital discharge. A follow-up period of 30 days was proposed as a practical standard, as the difference between 28 and 30 days is minimal. Given the acute nature of dengue and the low mortality rate, a 28-30 day timeframe was considered more feasible than a 90-day follow-up. In cases involving immunomodulators, extended follow-up was emphasised as necessary to capture potential delayed effects. However, maintaining mortality outcomes comparable to other acute infections remains an option, including both 28-day and 90-day mortality measures.

A prolonged observation period could introduce additional challenges, such as confounding due to mortality from other causes. The feasibility of extended follow-up presents several challenges. In settings where hospital and outpatient healthcare records are not integrated, tracking patients beyond discharge may be difficult. This is particularly problematic in low-resource environments, where consistent post-discharge monitoring is challenging and could affect the feasibility of mortality tracking in global clinical trials. Additionally, longer follow-up periods increase the risk of introducing noise from non-dengue-related mortality, further complicating the interpretation of outcomes.

2.1.3 Preliminary statement

We recommend reporting mortality during hospitalisation, assessed as "dead or discharged alive" as well as within 28 days post-discharge, assessed via hospital records, phone follow-up, or registries.

Assessment at 90 days post-discharge is optional, if longer-term treatment effects are of interest.

2.1.4 Hybrid consensus meeting and voting (24 February 2025)

Discussion:
28-day mortality was suggested as the standard measure. Concerns were raised that extending follow-up to 90 days could introduce confounding factors, as patients may die from causes unrelated to dengue. At-discharge mortality was highlighted as an important indicator of dengue-related outcomes.

All-cause vs. dengue-specific mortality: There was strong support for recording all-cause mortality, as it is a more reliable and robust measure in clinical trials compared to dengue-specific mortality. However, the cause of death should also be documented to distinguish dengue-related fatalities.

Standardization of time zero (Reference Point for Measurement): The importance of defining a clear reference point for mortality tracking in trials was emphasized. Since hospitalization duration varies widely, hospital discharge may not be a consistent starting point. Fever onset was suggested as a preferred reference point, as it is commonly used in dengue-related research.

Additional considerations: In certain settings, 90-day mortality could be assessed as an additional measure.

Final statement:

We recommend reporting all-cause mortality assessed as “dead or alive” at discharge (if hospitalised) and at 28 days since disease onset and randomisation.

Voting on the final statement for “mortality/survival” outcome:

Final statement for measurement “mortality/survival” outcome	N
agree	29/29 (100%)
disagree	-
abstain	-
do not have appropriate expertise to cast the vote	1

Conclusion: Agreement has been reached on measurement instrument

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2.2 “Platelet count” outcome measurement instrument report.

2.2.1 Identification of instruments

Several instruments were identified in the published literature and ongoing clinical trials for assessing “platelet count” in dengue patients. A preliminary expert review

was conducted prior to the online meeting to evaluate the relevance and feasibility of each instrument (see table below).

Pre-meeting expert voting on "platelet count" measurement instruments

Measurement Instrument	Type	Expert 1	Expert 2	Expert 3
As part of PELODS score	Scale/Questionnaire	Yes	Yes	Unvoted
As part of PRISM3 score	Scale/Questionnaire	Yes	No	Unvoted
Mean nadir platelet count	Lab	Yes	Yes	Yes
Increase/decrease in platelet count	Lab	Yes	No	Unvoted
Time taken to achieve a platelet count of 150,000 cells/mm³	Lab	Maybe	Yes	Yes
Time to normalization of platelet count	Lab	Maybe	Yes	Unvoted
Number of days prior to elevation of platelet count	Lab	Yes	No	Unvoted
Rate of decrease in platelet count	Lab	Maybe	Unvoted	Unvoted

Additional definitions reviewed:

Tomashek et al. classification for thrombocytopenia in dengue clinical trials:

- **Moderate thrombocytopenia:** Platelet count between ≥20,000 – ≤ 50,000 cells/mm³. Requires **more intensive observation** in a regular ward or transfer to **HDU/ICU**, depending on available facilities.
- Severe thrombocytopenia: Platelet count <20,000/mm³. Requires more intensive monitoring or transfer to HDU/ICU.
- Recommended measurement frequency: One platelet count daily during the critical phase to determine whether the patient meets the endpoint definition for moderate or severe thrombocytopenia.

Regulatory review:
Regulators expressed interest in establishing a threshold for platelet counts, noting significant variability across studies and trials.

2.2.2 Discussion during online meeting (5 February 2025)

During the meeting, it was discussed that while the Tomashek definition serves well in clinical settings, its use in clinical trials may present challenges due to its composite nature (the definition combines platelet count with other factors like HDU/ICU transfer, making it a composite outcome rather than a direct measure of platelet levels). Participants emphasized the importance of accounting for baseline

platelet counts at study entry to ensure accurate outcome measurement. It was also suggested that, for consistency with other parameters like mortality and ICU/HDU admission, platelet count should be framed as an adverse outcome in the context of clinical trials.

2.2.3 Preliminary statement

Platelet count is defined as the absolute number of platelets (cells/mm³) measured via laboratory testing. It is recommended to assess it daily (if possible) during the acute phase of dengue infection to evaluate thrombocytopenia severity and trends over time. Mean nadir platelet count (lowest recorded platelet count during the acute phase) also must be recorded.

The following categorisation is recommended:

- Moderate thrombocytopenia: ≥20,000 – ≤ 50,000 cells/mm³
- Severe thrombocytopenia: < 20,000 cells/mm³

2.2.4 Hybrid consensus meeting and voting (24 February 2025)

Discussion:
Platelet count was identified as a highly variable measure, raising concerns about its strength as a statistical outcome in clinical trials. Despite these statistical limitations, the group emphasized the continued clinical significance of platelet count, supporting its inclusion in trial measurements.

There was debate regarding the necessity of measuring nadir platelet count. Concerns were raised about reliably capturing the nadir. However, the clinical value of this measurement in understanding disease progression was strongly recognized. The group concluded that both nadir and upward trends should remain as integral components of platelet count outcome assessment.

Measurement frequency and timing: Defining appropriate frequency and timing for platelet measurements was extensively discussed. While daily measurements were initially proposed to capture platelet fluctuations thoroughly, concerns about feasibility led to suggestions for less frequent measurements. A consensus emerged recommending at least three platelet measurements between days 4 to 8 of illness, recognizing this period as critical for capturing clinically relevant trends, particularly around day 6, typically representing the nadir. Alternative comparisons between timeframes (e.g., days 3–5 versus 8–9) were also considered as potential methods to effectively document platelet dynamics.

Final statement:

Platelet count is defined as the absolute number of platelets (cells/mm³) measured via laboratory testing. We recommended assessing it daily (if possible, but at least three times between days 4 and 8 since disease onset) during the acute phase of

dengue infection to evaluate thrombocytopenia severity and trends over time. Nadir platelet count (lowest recorded platelet count during the acute phase) also must be recorded.

The following categorisation is recommended:

- Moderate thrombocytopenia: ≥20,000 – ≤ 50,000 cells/mm^3
- Severe thrombocytopenia: < 20,000 cells/mm^3

Voting on the final statement for "Platelet count" outcome:

Final statement for measurement "platelet count" outcome	**N**
agree	24/26 (92,3%)
disagree	1/26 (3,85%)
abstain	1/26 (3,85%)
do not have appropriate expertise to cast the vote	1

Conclusion: Agreement has been reached on measurement instrument

2.3 Progression to severe disease

Progression to severe disease is not an outcome and was not included in the Delphi voting process. It is a composite term introduced to collectively describe severe dengue complications.

Progression to severe disease is defined as the development of any one of the following severe complications during the course of illness: 'shock', 'severe bleeding', 'severe fluid leakage', 'organ failure' and/or 'need for ICU/HDU care'

We recommend measuring each of these outcomes independently and reported separately, rather than as a composite measure.

2.3.1 "Need for ICU/HDU care" outcome measurement instrument report.

2.3.1.1 Identification of instruments

Several instruments were identified in the published literature and ongoing clinical trials for assessing "need for ICU/HDU care" in dengue patients. A preliminary expert review was conducted prior to the online meeting to evaluate the relevance and feasibility of each instrument (see table below).

Pre-Meeting expert voting on "Need for ICU/HDU care" measurement instruments

Measurement Instrument	Type	Expert 1	Expert 2	Expert 3
Date of admission and discharge	Clinical assessment	Yes	Yes	Yes
Days of HDU stay	Clinical assessment	Yes	Yes	Yes

2.3.1.2 Discussion during online meeting (5 February 2025)

During discussion it was highlighted that HDU definitions differ across settings. In some regions, HDUs function like acute care units with enhanced monitoring but may lack critical care capabilities found in ICUs. Limited ICU capacity may prevent admissions in some settings. Therefore, organ support–based criteria, rather than actual ICU admission status, may be considered as a measurement instrument for the outcome.

2.3.1.3 Preliminary statement

A patient is classified as 'need for ICU/HDU care' if they require **one or more** of the following life-sustaining interventions* **at any point during hospitalisation, regardless** of actual ICU/HDU admission status.

***Interventions:**
Respiratory Support

- Invasive mechanical ventilation
- Non-invasive ventilation (e.g., CPAP, BiPAP)
- High-flow oxygen therapy

Cardiovascular Support

- Administration of vasopressors or inotropes to manage shock or persistent hypotension

(Patient meets this definition if they exhibit systolic blood pressure (SBP) below the age- and sex-adjusted threshold (SBP < 90 mmHg or MAP < 65 mmHg in adults; age-specific cutoffs for children) and remain hypotensive after receiving an initial IV fluid bolus of ≥ 20 mL/kg (e.g., Ringer's lactate, normal saline) over ≤ 30 minutes. Persistent hypotension is confirmed when additional fluid boluses (≥ 10 mL/kg per bolus) or continuous IV fluids at ≥ 2 times maintenance rate are required. Patients whose hypotension resolves after a single bolus or those with hypotension due to non-infectious causes (e.g. haemorrhage, cardiogenic shock) are excluded from this definition)

Renal Support

- Initiation of acute dialysis or continuous renal replacement therapy due to kidney failure

Neurological Support

- Reduced consciousness (GCS ≤ 8) requiring airway protection
- Seizures requiring intravenous antiseizure medications

2.3.1.4 Hybrid consensus meeting and voting (24 February 2025)

Discussion:
During the hybrid meeting, participants reviewed and discussed the proposed outcome measurement statement for "Need for ICU/HDU care." The discussion focused on refining the outcome definition to ensure both clinical relevance and feasibility across diverse healthcare settings.

There was an agreement that ICU admission/duration of stay is highly variable across healthcare settings and may reflect institutional practices more than clinical need. Despite this, participants agreed that ICU/HDU admission should be recorded as an important resource-use outcome, given the absence of alternative metrics to capture the burden of critical illness. Furthermore, ICU admission was recognized as a major clinical event, associated not only with significant resource utilization but also with increased patient risk. However, it was noted that ICU need may not always reflect dengue severity, especially in elderly patients or those with comorbidities. Participants discussed defining clinical criteria for ICU need, allowing for standardized outcome measurement even in settings without formal ICU infrastructure.

The final measurement instrument structure was approved by participants, with strong support for an integrated approach that captures both resource utilization and severity of illness through a combination of ICU/HDU admission status and organ support indicators.

Additional considerations:
The importance of standardizing the definition of respiratory support, including high-flow oxygen therapy, was emphasized.

Final statement:

A patient is classified as 'need for ICU/HDU care' if they were admitted/transferred to ICU/HDU and/or required one or more of the following life-sustaining interventions* at any point during hospitalisation, regardless of actual ICU/HDU admission status.

*__Interventions__:
Respiratory Support
- Invasive mechanical ventilation
- Non-invasive ventilation (e.g., new requirement of CPAP, BiPAP)
- High-flow oxygen therapy

Cardiovascular Support
- Administration of vasopressors or inotropes to manage shock or persistent hypotension

(Patient meets this definition if they exhibit systolic blood pressure (SBP) below the age- and sex-adjusted threshold (SBP < 90 mmHg or MAP < 65 mmHg in adults; age-specific cutoffs for children) and remain hypotensive after receiving an initial IV fluid bolus of ≥ 20 mL/kg (e.g., Ringer's lactate, normal saline) over ≤ 30 minutes.
Persistent hypotension is confirmed when additional fluid boluses (≥ 10 mL/kg per bolus) or continuous IV fluids at ≥ 2 times maintenance rate are required. Patients whose hypotension resolves after a single bolus or those with hypotension due to non-infectious causes (e.g. haemorrhage, cardiogenic shock) are excluded from this definition)

Renal Support
- Initiation of acute dialysis or continuous renal replacement therapy due to kidney failure

Neurological Support
- Reduced consciousness (GCS ≤ 8)
- Seizures requiring intravenous antiseizure medications

Organ failure and severe bleeding
- As per suggested assessment for the relevant outcome

Voting on the final statement for “need for ICU/HDU care” outcome:

Final statement for measurement “Need for ICU/HDU care” outcome	N
agree	24/24 (100%)
disagree	-
abstain	-
do not have appropriate expertise to cast the vote	3

Conclusion: Agreement has been reached on measurement instrument

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2.3.2 “Organ dysfunction” outcome measurement instrument report

2.3.2.1 Identification of instruments

Several instruments were identified in the published literature and ongoing clinical trials for assessing “organ failure” in dengue patients. A preliminary expert review was conducted prior to the online meeting to evaluate the relevance and feasibility of each instrument (see table below).

Pre-meeting expert voting on “organ failure” measurement instruments

Measurement Instrument	Type	Expert 1	Expert 2	Expert 3
Modified Sequential Organ Failure Assessment (mSOFA) score	Scale/Questionnaire	Yes	Yes	Yes
Pediatric Logistic Organ Dysfunction (PELOD)score	Scale/Questionnaire	Yes	Yes	Unvoted

2.3.2.2 Discussion during online meeting (5 February 2025)

The overall discussion on organ failure assessment highlighted a strong consensus regarding the utility of the mSOFA score as a standardized tool for evaluating organ failure in clinical trials. Its versatility in both adult and pediatric populations was widely acknowledged, and many participants agreed on its potential to harmonize outcome measures across diverse settings. However, several critical considerations and challenges were discussed.

Considerations**:**

- While the SOFA score’s utility was broadly acknowledged, concerns were raised regarding its limited application in dengue trials. Participants

emphasized the need for further validation to ensure its suitability for dengue-specific clinical contexts.
- Success with the modified organ failure assessment would be reflected in trends over time rather than absolute values. An improving score would indicate patient recovery, while worsening scores would reflect disease progression.

Other instruments:
- ALT thresholds: The distinction between organ failure and severe organ impairment was also discussed. For example, the WHO ALT cut-off of ≥ 1,000 (IU/L) indicates severe liver involvement but does not necessarily define liver failure. This highlights the need for more specific criteria to accurately differentiate levels of organ dysfunction in dengue patients.
- Suggestions were made regarding the inclusion of vasopressor support criteria to enhance the score's sensitivity in detecting severe cases.
- Participants suggested evaluating additional biomarkers such as bilirubin to assess for acute liver injury in dengue patients.

2.3.2.3 Preliminary statement

We recommend assessing organ failure as the dysfunction of **one or more vital organ systems** requiring medical intervention, assessed using the modified Sequential Organ Failure Assessment (mSOFA) score adapted for dengue. **Each organ system component of mSOFA score should be recorded and reported independently** to accurately capture the nature and cause of organ failure.

2.3.2.4 Hybrid consensus meeting and voting (24 February 2025)

Discussion:
The need to distinguish organ dysfunction from organ failure and to capture dysfunction before ICU admission to better understand disease progression was emphasised. A broader term, "organ dysfunction," was suggested to allow earlier and more comprehensive measurement. There was agreement that organ dysfunction should be assessed at randomization and at pre-defined intervals to track disease progression.

During the hybrid meeting, the use of mSOFA was reaffirmed as the primary instrument for assessing organ dysfunction. Discussions further addressed parameters included in the mSOFA score:
- Respiratory: Oxygen saturation was identified as a key marker.
- Coagulation: Platelet count alone was not considered a reliable measure of coagulation.
- Hepatic: Bilirubin was recommended for inclusion across all sites.

- Renal: Renal function (e.g., creatinine) should be assessed, but limitations in availability were noted, particularly in Phase 3 trials.

Timing: Organ dysfunction should be assessed at randomization and at least three times between Days 4–8. An additional suggestion was made to assess organ dysfunction 24–28 hours post-fever clearance to monitor recovery. Consensus supported recording both the highest mSOFA score during the study and score trends over time.

Additional notes**:** Pediatric adaptations and system-specific parameters should be considered where appropriate.

Additional parameters:

- ALT/AST levels >1000 U/L were acknowledged as markers of liver injury but not definitive for failure. In Phase II trials, ALT/AST may be monitored for safety rather than as primary outcomes.

Final statement:

Organ failure is defined as the dysfunction of one or more vital organ system assessed using the modified Sequential Organ Failure Assessment (mSOFA) score, adapted for dengue at least three times, at randomization and between 4 and 8 days from symptom onset. Each organ system component of mSOFA score should be recorded and reported independently to accurately capture the nature and cause of organ failure. *It is suggested to measure AST and ALT when possible as an exploratory outcome, but it should not be used alone to define liver failure.

Voting on the final statement for “Organ dysfunction” outcome:

Final statement for measurement “Organ dysfunction” outcome	**N**
agree	19/23 (83%)
disagree	1/23 (4,35%)
abstain	3 (13%)
do not have appropriate expertise to cast the vote	4

Conclusion: Agreement has been reached on measurement instrument

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2.3.3 "Severe bleeding" outcome measurement instrument report

2.3.3.1 Identification of instruments

Several instruments were identified in the published literature and ongoing clinical trials for assessing "severe bleeding" in dengue patients. A preliminary expert review was conducted prior to the online meeting to evaluate the relevance and feasibility of each instrument (see table below).

Pre-meeting expert voting on "severe bleeding" measurement instruments

Measurement instrument	Type	Expert 1	Expert 2	Expert 3
WHO bleeding scores	Scale/Questionnaire	maybe	Yes	maybe
Pictorial Blood loss Assessment Charts (PBACs)	Scale/Questionnaire	maybe	no	no
Evidence of bleeding	Clinical Assessment	yes	no	maybe
Bleeding Time (minutes)	Clinical Assessment	yes	no	no
Positive tourniquet test	Clinical Assessment	no	no	no
Requirement of standard haemostatic replacement therapy	Clinical Assessment	yes	yes	yes
Hb, Haematocrit	Lab	yes	maybe	no

Additional definitions considered:

A dengue-specific definition of severe bleeding adapted from **Tomashek et al.** was reviewed. This definition includes the following criteria:
Clinical trial participant has any one of the following four types of bleeding listed below:

- Bleed into a critical organ (e.g., CNS bleed)
- Bleed leading to hemodynamic instability
- Bleed resulting in death or permanent disability (e.g., CNS bleed; intraocular bleed)
- Bleed that results in need for blood transfusion AND requires more intensive monitoring in an ICU or HDU

When collecting data to describe and determine the severity of bleeding among clinical trial participants, investigators should consider the following:

- Finding that a type and cross match was ordered does not serve as a reliable indicator of bleeding severity. That is, it does not meet criteria as a local intervention on its own.
- Periorbital bleed with periorbital swelling can be a moderate bleed if it requires need for pressure compress (see large skin/injection site bleed needing pressure compress).
- "Need for blood transfusion" should be defined as needing whole blood or packed red blood cells. If fresh frozen plasma, platelets or factor concentrates are given without whole blood or packed red blood cells then it

is unlikely that the bleed is clinically severe. Prophylactic platelet transfusions or fresh frozen plasma given for clinical laboratory values (i.e., no clinical indication) are not case defining

2.3.3.2 Discussion during online meeting (5 February 2025)

The Tomashek definition of severe bleeding was favoured across all groups. Participants noted that Tomashek's guidelines focus on clinically relevant bleeding that requires intervention, making them more suitable compared to broader, non-specific bleeding definitions used in other diseases.

Limitations and considerations:
Concealed Bleeding: The challenge of identifying occult (hidden) bleeding was discussed. Participants highlighted that such bleeding may not present immediate hematologic changes (e.g. no drop in haematocrit due to haemoconcentration) but can be inferred through clinical signs like hemodynamic instability and response to blood transfusion

Use of haematological scales: It was suggested to explore haematological society guidelines (e.g. ISTH Bleeding Scale) for potential adaptation to dengue trials. However, concerns were raised about the over-reliance on platelet transfusions in haematology settings, which may not be appropriate for dengue management.

Considerations: Caution was expressed regarding adopting haematological scales, emphasizing that dengue-specific guidelines should take precedence to avoid unnecessary interventions, such as over-transfusion of platelets.

The BASIC score: was discussed as an alternative, particularly in pediatric populations. While it incorporates many elements of Tomashek's definition, it was considered more complex and less practical for broader clinical application.

2.3.3.3 Preliminary statement

Severe bleeding is assessed as **any** bleeding event that results in hemodynamic instability, requires blood transfusion, involves a critical organ, or leads to death.

A patient is classified as having severe bleeding if they meet **any** of the following criteria:
Fatal bleeding that directly results in death.
Symptomatic bleeding in critical areas or organs, such as:
- Intracranial (e.g. cerebral haemorrhage)
- Intraspinal
- Intraocular (leading to vision impairment)
- Retroperitoneal
- Intra-articular

Pericardial
Intramuscular with compartment syndrome

Hemodynamic instability presenting as bleeding causing a fall in systolic blood pressure (SBP) below absolute cutoffs:
Adults: SBP < 90 mmHg
Children <1 year: SBP < 70 mmHg
Children 1–10 years: SBP < [70 + (2 × age in years)] mmHg
Children >10 years: SBP < 90 mmHg

or a heart rate >110 beats per minute, necessitating medical intervention.

Bleeding leading to a decrease in haemoglobin levels of ≥2 g/dL (1.24 mmol/L) or necessitating the transfusion of 2 or more units of whole blood or red cells.

2.3.3.4 Hybrid consensus meeting and voting (24 February 2025)

Discussion:
During the hybrid consensus meeting, the definition and measurement strategy for severe bleeding were refined through structured discussion. The following issues were addressed:

Haemoglobin decrease:

- Haemoglobin drop may not always be direct to bleeding in dengue.
- A universal haemoglobin threshold (g/dL) independent of age may not be appropriate.
- Occult bleeding could lead to a delayed drop in haemoglobin

Blood Pressure Cut-offs: Isolated hypotension was considered insufficient to define severe bleeding due to multiple potential causes
Participants proposed that criteria 3 (hemodynamic instability) and 4 (haemoglobin drop/transfusion) should be considered together, rather than separately. It was noted that WHO guidelines already align with this approach, highlighting the importance of harmonization between initiatives.

There was a suggestion to consider renaming the outcome to “Clinically significant bleeding”, to encompass severe events that do not meet all criteria for “severe bleeding” but still require medical intervention. However, this would constitute a distinct outcome, which was not included in the Delphi voting process.

Final statement:

Severe bleeding is defined as any bleeding event that results in hemodynamic instability, requires blood transfusion, involves a critical organ, or leads to death.

A patient is classified as having severe bleeding if they meet the following criteria:

Either:

1. Bleeding that directly results in death.

OR

2. Symptomatic bleeding in critical areas or organs, such as:
    - Intracranial (e.g., cerebral hemorrhage)
    - Intraspinal
    - Intraocular (leading to vision impairment)
    - Retroperitoneal
    - Intra-articular
    - Pericardial
    - Intramuscular with compartment syndrome

OR

3. Hemodynamic instability presenting as bleeding necessitating medical intervention causing a fall in systolic blood pressure (SBP) below absolute cutoffs:
    - Adults: SBP < 90 mmHg
    - Children <1 year: SBP < 70 mmHg
    - Children 1–10 years: SBP < [70 + (2 × age in years)] mmHg
    - Children >10 years: SBP < 90 mmHg

Or a heart rate >110 beats per minute necessitating medical intervention

AND

4. Bleeding, leading to a decrease in haemoglobin levels of ≥2 g/dL (1.24 mmol/L) or necessitating the transfusion of 2 or more units of whole blood or red cells.

Voting on the final statement for "severe bleeding" outcome:

Final statement for measurement "Severe bleeding" outcome	**N (%)**
agree	19/24 (79%)
disagree	2/24 (8,3%)
abstain	3/24 (12,5%)
do not have appropriate expertise to cast the vote	3

Conclusion: Agreement has been reached on measurement instrument

2.3.4 "Severe fluid plasma/leakage" outcome measurement instrument report

2.3.4.1 Identification of instruments

Several instruments were identified in the published literature and ongoing clinical trials for assessing "severe fluid/plasma leakage" in dengue patients. A preliminary expert review was conducted prior to the online meeting to evaluate the relevance and feasibility of each instrument (see table below).

Pre-meeting expert voting on "severe fluid/plasma leakage" measurement instruments

Measurement instrument		**Type**	**Expert 1**	**Expert 2**	**Expert 3**
Presence of free fluid in the peritoneal cavity (gall bladder wall thickness, ascites), pleural cavity	Ultra sound scan	Instrumental examination	yes	yes	yes
	Xray		yes	maybe	no
	MRI		no	no	no
plasma markers (e.g. Syndecan-1)		Lab	maybe	maybe	no
15% change in haematocrit		Lab	yes	maybe	yes
plasma concentration of albumin, cholesterol		Lab	yes	maybe	no
Return of PCV to normal level,		Lab	maybe	maybe	no
Pleural effusion		Clinical Assessment	yes	yes	yes
Stabilising vital signs		Clinical Assessment	maybe	yes	no
Splitting of second heart sounds (S2)		Clinical Assessment	maybe	no	no
Diuresis		Clinical Assessment	yes	maybe	no
Requirement of crystalloid, colloid boluses, blood transfusions		Clinical Assessment	yes	yes	no

Additional definitions considered:

A definition for "severe plasma leakage" from **Tomashek et al.** for its applicability was also reviewed. This definition includes the following criteria: Clinical trial participant has any one of the following four types of bleeding listed below:

Clinical trial participant has evidence of hemodynamic instability or respiratory compromise, and evidence of plasma leakage defined by:

1.) >20% change in haematocrit during the illness; and/or
2.) evidence of a new pleural effusion, pericardial effusion, and ascites on ultrasound or x-ray.

2.3.4.2 Discussion during online meeting (5 February 2025)

Due to time constraints, “severe fluid/plasma leakage” measurement instruments were not discussed during the online meeting.

2.3.4.3 Preliminary statement

We suggest measuring ‘severe plasma leakage’ assessing a significant and measurable loss of intravascular fluid into third spaces, confirmed by laboratory and imaging criteria.
Severe plasma leakage will be confirmed in a patient if they meet **at least one** of the following independent criteria:

1. Evidence of plasma leakage on imaging
    - New pleural effusion (≥1 cm depth on ultrasound OR detected on X-ray)
    - New pericardial effusion (confirmed by ultrasound)
    - New ascites (≥1 cm depth on ultrasound)
2. Haemoconcentration confirming plasma leakage
    - ≥20% increase in haematocrit compared to baseline
    - ≥15% decrease in haematocrit following IV fluid resuscitation

2.3.4.4 Hybrid Consensus Meeting and Voting (24 February 2025)

Discussion:
The group debated whether severe plasma leakage should require the presence of shock or if haemoconcentration alone could be sufficient. Opinions differed: some participants defined severe plasma leakage as the combination of shock and haemoconcentration, while others argued that shock should not be a mandatory criterion, particularly in late-stage cases.

Concerns were raised that a 15% haematocrit decrease after intravenous fluid administration is problematic, as the degree of change depends on the amount and type of fluid given. As an alternative marker, a 20% haematocrit decrease after day 10 was suggested, acknowledging that many late-presenting patients may not have an initial baseline measurement.

The group also debated whether baseline haematocrit should be measured at the time of randomization. Concerns were expressed regarding patients who arrive late in the disease course and may lack an initial haematocrit value.
Imaging (e.g., ultrasound) should be performed where feasible to confirm “severe plasma leakage”

Final statement:

We suggest measuring 'severe plasma leakage' defined as a clinically significant and/or measurable loss of intravascular fluid into third spaces, by clinical examination at randomization and every other day between days 4 and 8* AND imaging findings, if possible.

*Severe plasma leakage will be confirmed if at least one of the following independent criteria is met:
Either:
1. Evidence of significant extravascular fluid accumulation on clinical examination (and ideally confirmed by imaging)
- (New pulmonary pleural effusion or new large volume ascites) causing respiratory compromise

OR
2. Hemoconcentration confirming significant plasma leakage
- ≥20% increase in hematocrit compared to baseline (if available)

Voting on the final statement for "severe fluid plasma/leakage" outcome:

Final statement for measurement "Severe fluid plasma/leakage" outcome	**N**
agree	21/25 (84%)
disagree	1/25 (4%)
abstain	3/25 (12%)
do not have appropriate expertise to cast the vote	0

Conclusion: Agreement has been reached on measurement instrument

2.3.5 “Development of shock” outcome measurement instrument report

2.3.5.1 Identification of instruments

Several instruments were identified in the published literature and ongoing clinical trials for assessing “development of shock” in dengue patients. A preliminary expert review was conducted prior to the online meeting to evaluate the relevance and feasibility of each instrument (see table below).

Pre-meeting expert voting on “development of shock” measurement instruments

Measurement instrument	Type	Expert 1	Expert 2	Expert 3
Pulse pressure of ≤20 mmHg	Scale/Questionnaire	yes	yes	yes
Drop in the systolic blood pressure of 30mmHg or more	Scale/Questionnaire	maybe	yes	yes

Additional definition reviewed:

ISARIC CRF shock definition: “Shock refers to circulatory failure, causing inadequate oxygen delivery to meet cellular metabolic needs. It is defined by the presence of any two of the following:

- evidence of hypoperfusion (e.g. capillary refill >2 seconds, cold clammy skin, and rapid/weak pulse, altered mental status)
- narrow pulse pressure (less than or equal to 20mmHg)
- hypotension for age
- tachycardia (>100bpm)

2.3.5.2 Discussion during online meeting (5 February 2025)

Review of ISARIC definition:
One of the concerns raised were about inclusion of tachycardia as a key indicator. It was noted that in adults with dengue shock, heart rates often do not rise significantly, typically remaining around 80-90 bpm. Shock in dengue primarily manifests through hypoperfusion to organs, rather than a significant increase in heart rate. This raised concerns about tachycardia being a late sign of shock, which may reduce its effectiveness as an early measurement instrument. Another concern was raised towards “evidence of hyperperfusion” that it could be too subjective.

Pulse pressure: It was emphasized that pulse pressure is a simple, feasible, and objective measurement tool. It aligns with WHO definitions and is widely used, especially in paediatrics. A pulse pressure below 20 mmHg often triggers clinical interventions such as fluid boluses. However, in adults, pulse pressure narrowing tends to occur late, necessitating immediate intervention.

Shock index**:** The Shock Index (heart rate divided by systolic blood pressure) was noted for its ease of collection and effectiveness in dengue trials. It was highlighted that heart rate increases often precede blood pressure drops, making this a practical early indicator.
Systolic pressure**:** concerns were raised that a drop in systolic pressure is not useful without knowledge of the baseline blood pressure.

Lactate as a marker: The potential use of lactate as a marker of tissue hypoperfusion was debated. While lactate levels were associated with worse outcomes in pediatric populations, results were often inconsistent due to severe patient shutdown. Additionally, lactate measurements may not be readily available in resource-limited settings.

2.3.5.3 Preliminary statement

We suggest assessing 'development of shock' via circulatory failure with inadequate oxygen delivery to tissues, classified into compensated and decompensated shock measuring objective hemodynamic parameters, including pulse pressure, systolic blood pressure, and clinical signs of hypoperfusion.

A patient is classified as having shock if they meet **any** of the following:

1. Objective Hemodynamic Marker **(any one of the following):**
    - Pulse pressure ≤ 20 mmHg
    - Systolic Blood Pressure (SBP) below absolute cutoffs:
        - Adults: SBP < 90 mmHg
        - Children <1 year: SBP < 70 mmHg
        - Children 1–10 years: SBP < [70 + (2 × age in years)] mmHg
        - Children >10 years: SBP < 90 mmHg
    - Shock Index ≥ 1.0 (Heart Rate / SBP ≥ 1.0 in adults and children >5 years)
2. Objective Evidence of Hypoperfusion **(any one of the following):**
    - Capillary refill time > 2 seconds
    - Urine output < 0.5 mL/kg/hour for ≥ 6 hours

2.3.5.4 Hybrid consensus meeting and voting (24 February 2025)

Discussion:
The group held an in-depth discussion on the parameters to be included in the definition of shock. Concerns were raised about the reliability of using blood pressure (BP) alone, as some patients may have a baseline low BP, while others may present with restlessness and shock without hypotension.

The use of the Shock Index was proposed, as heart rate may serve as a more consistent indicator in certain cases. Additionally, Mean Arterial Pressure (MAP) was suggested as an alternative measurement parameter.

The group emphasized the importance of developing a robust yet flexible clinical definition. It was agreed that shock should be defined by the presence of either Pulse Pressure ≤ 20 mmHg, Shock Index ≥ 1.0, or Systolic Blood Pressure (SBP) below absolute cutoffs, in combination with at least one objective indicator of hypoperfusion (listed below).

Additional discussion points:

- Lactate was discussed as an additional marker of tissue hypoperfusion. However, due to feasibility concerns in low-resource settings, it was agreed that lactate measurement should be included only when resources allow.

- There was debate on whether the decision to initiate treatment should be included in the definition. Industry representatives emphasized that shock remains a clinical diagnosis and should not be defined solely by numeric thresholds. The group agreed that while intervention decisions should not be a primary defining factor, they may be considered supportively in assessing whether a patient is in shock.

Final statement:

'Development of shock' defined as circulatory failure with inadequate oxygen delivery to tissues, classified into compensated and decompensated shock, and is assessed by measuring objective hemodynamic parameters, including pulse pressure, systolic blood pressure, and clinical signs of hypoperfusion.
A patient is classified as having shock if they meet the following objective hemodynamic markers:

Either:

1. Pulse pressure ≤ 20 mmHg OR Shock Index ≥ 1.0 (Heart Rate / SBP ≥ 1.0 in adults and children >5 years)

OR

2. Systolic Blood Pressure (SBP) below absolute cutoffs:
   - Adults: SBP < 90 mmHg or MAP<60
   - Children <1 year: SBP < 70 mmHg
   - Children 1–10 years: SBP < [70 + (2 × age in years)] mmHg
   - Children >10 years: SBP < 90 mmHg

AND

3. In addition to meeting one of the above criteria, objective evidence of hypoperfusion with at least 1 of the following:

- Capillary refill time > 2 seconds
- Urine output < 0.5 mL/kg/hour for ≥ 6 hours if feasible
- Cold/clammy peripheries

- Agitation or altered mental state

Voting on the final statement for “development of shock” outcome:

Final statement for measurement “Development of shock” outcome	**N (%)**
agree	23/25 (92%)
disagree	2/25 (8%)
abstain	0
do not have appropriate expertise to cast the vote	25

Conclusion: Agreement has been reached on measurement instrument

2.4 Need for hospitalisation outcome measurement instrument report.

2.4.1 Identification of instruments

In the published literature and ongoing clinical trials “need for hospitalisation” in dengue patients was assesed as “hospitalisation rate”, “admission to hospital” and “duration of hospitalisation”.

Regulatory review:
Mortality combined with the need for hospitalisation is likely to be accepted by regulators as these outcomes are measurable across all settings. Harmonisation is needed in what is defined under “need for hospitalisation”

2.4.2 Discussion during online meeting (5 February 2025)

Due to time constraints, “need for hospitalisation” measurement instruments were not discussed during the online meeting.

2.4.3 Preliminary statement

We suggest assessing ‘need for hospitalisation’ defined as the requirement for inpatient care **at any point of clinical trial period**, based on the WHO criteria***, regardless** of actual hospitalisation status.

*Criteria (any of the following):
1. Warning Signs:
- Severe abdominal pain or tenderness
- Persistent vomiting (≥3 episodes per hour or ≥6 episodes in 6 hours)
- Clinical evidence of fluid accumulation (pleural effusion, ascites, or gallbladder wall thickening confirmed by ultrasound)
- Mucosal bleeding (e.g., gum bleeding, epistaxis, gastrointestinal or genitourinary bleeding)
- Lethargy or restlessness
- Liver enlargement >2 cm

2. Signs and symptoms related to hypotension:
- Profuse perspiration, fainting, or postural hypotension
- Cold extremities or hypotension (SBP <90 mmHg in adults, age-specific cutoff in children):
    - Children <1 year: SBP <70 mmHg
    - Children 1–10 years: SBP < [70 + (2 × age in years)] mmHg
    - Children >10 years: SBP <90 mmHg
- Pulse pressure ≤20 mmHg
- Capillary refill time >2 seconds

3. Spontaneous bleeding:
   - Active bleeding independent of platelet count
   - Haemoglobin drop ≥2 g/dL requiring transfusion
4. Organ impairment:
   - Renal impairment (Creatinine >2.0 mg/dL or urine output <0.5 mL/kg/hour for ≥6 hours)
   - Liver impairment (AST or ALT ≥1,000 IU/L, aligned with WHO severe dengue criteria)
   - Neurological symptoms (Altered mental status, new-onset seizures, GCS ≤8)
   - Cardiac impairment (Chest pain, cyanosis, respiratory distress requiring oxygen support)
5. Specified laboratory and imaging findings:
   - Rising haematocrit concurrent with a rapid platelet count drop
   - Pleural effusion, ascites, or gallbladder wall thickening confirmed by ultrasound or X-ray

2.4.4 Hybrid consensus meeting and voting (24 February 2025)

Discussion:
The primary issue raised by the group was the variability in hospitalization criteria across different settings, which makes standardization challenging.
Participants emphasized the importance of distinguishing between hospital admissions due to trial protocols and those based on clinical necessity. It was agreed that trial-related hospitalizations should be documented separately to avoid confounding the interpretation of clinical outcomes.

The group also discussed the definition of hospitalization, specifically whether it should include any inpatient admission or only those involving an overnight stay.

To enhance the specificity of hospitalization as an outcome, the group agreed on the importance of differentiating between dengue-related and unrelated hospitalizations. A consensus was reached on the following:

- For clinical assessment, hospitalization should be recorded only when at least one WHO-defined warning sign is present.
- For resource utilization analysis, hospitalization should be recorded regardless of the presence of warning signs.

Final statement:

We recommend measuring 'need for hospitalisation' during the acute illness episode by two separate parameters:
(a) admitted to hospital for any medical reason (for healthcare utilization purposes);

(b) developed one or more warning signs proposed by the WHO, regardless of actual hospitalisation status.

Voting on the final statement for "Need for hospitalisation" outcome:

Final statement for measurement "Need for hospitalisation" outcome	N (%)
agree	20/24 (83%)
disagree	4/24 (17%)
abstain	0
do not have appropriate expertise to cast the vote	0

Conclusion: Agreement has been reached on measurement instrument

2.5 “Viral load” outcome measurement instrument report.

2.5.1 Identification of instruments

Several instruments were identified in the published literature and ongoing clinical trials for assessing “viral load” in dengue patients. A preliminary expert review was conducted prior to the online meeting to evaluate the relevance and feasibility of each instrument (see table below).

Pre-meeting expert voting on “viral load” measurement instruments

Measurement Instrument	Type	Expert 1	Expert 2
Area under the log-transformed viremia curve (AUC)	Lab	Yes	Yes
Changes of viral load over time	Lab	Yes	Yes
qPCR	Lab	Yes	Maybe
Reduction of DENV RNA from baseline	Lab	Yes	Maybe
NS1 cell-based titration (NSET) assay	Lab	Yes	Maybe
Peak of viremia curve	Lab	Maybe	Yes

Regulatory review:
Viral load measurement is relevant for evaluating antivirals but may have limited utility for interventions such as immunomodulators. It does not always correlate with clinical symptoms, which restricts its applicability in certain contexts. It would not be accepted as a primary outcome measure without an accompanying clinical endpoint in efficacy trials.

2.5.2 Discussion during online meeting (5 February 2025)

Due to time constraints, “viral load” measurement instruments were not discussed during the online meeting.

2.5.3 Preliminary statement

We suggest measuring viral load as the quantification of dengue virus RNA in blood, measured using real-time quantitative PCR (qPCR) at standardised time points: Day 1–2 (baseline), Day 4–5 (midpoint), Day 7 (late measurement) and at the time of hospital discharge*. We recommend reporting levels collected at each point individually as well as change in viral load over time and area under the viremia curve.

*Assessment at additional time points is optional, if feasible and resources allow.

2.5.4 Hybrid consensus meeting and voting (24 February 2025)

Discussion:

Participants agreed that no single measurement instrument is currently feasible for universal use in every phase 3 clinical trial. The discussion focused on defining an appropriate measurement timeframe for settings where resources permit. Consensus was reached to recommend measuring viral load before randomisation, and at 24 and 48 hours.

Final statement:

If feasible and resources allow, we recommend measuring viral load as the quantification of dengue virus RNA in blood, by real-time quantitative PCR (qPCR) before randomisation, at 24 and 48 hours. We recommend reporting individual viral load measurements separately, in addition to change in viral load over time and area under the viremia curve. Viral load data should always be reported alongside day of illness.

Voting on the final statement for "viral load" outcome:

Final statement for measurement "Viral load" outcome	N (%)
agree	26/28 (93%)
disagree	2/28 (7%)
abstain	0
do not have appropriate expertise to cast the vote	2

Conclusion: Agreement has been reached on measurement instrument

3. Hybrid meeting voting matrix

Outcome statement	Agree	Disagree	abstain	Do not have appropriate expertise to cast the vote	Result
Mortality	29/29 (100%)	0	0	1	Agreement has been reached on measurement instrument
Platelet count	24/26 (92%)	1/26 (4%)	1/26 (4%)	1	
Need for ICU/HDU	24/24 (100%)	0	0	3	
Organ failure	19/23 (83%)	1/23 (4%)	3/23 (13%)	4	
Development of shock	23/25 (92%)	2/25 (8%)	0	3	
Severe bleeding	19/24 (79%)	2/24 (8%)	3/24 (13%)	3	
Severe fluid leakage	21/25 (84%)	1/25 (4%)	3/25 (12%)	0	
Need for hospitalisation	20/24 (83%)	4/24 (17%)	0	0	
Viral load	26/28 (93%)	2/28 (7%)	0	1	

4.Final statements

Mortality/survival

We recommend reporting all-cause mortality assessed as “dead or alive” at discharge (if hospitalised) and at 28 days since disease onset and randomisation.

Platelet count

Platelet count is defined as the absolute number of platelets (cells/mm^3) measured via laboratory testing. We recommended assessing it daily (if possible, but at least three times between days 4 and 8 since disease onset) during the acute phase of dengue infection to evaluate thrombocytopenia severity and trends over time. Nadir platelet count (lowest recorded platelet count during the acute phase) also must be recorded.

The following categorisation is recommended:

- Moderate thrombocytopenia: ≥20,000 – ≤ 50,000 cells/mm^3
- Severe thrombocytopenia: < 20,000 cells/mm^3

Progression to severe dengue

Progression to severe disease is defined as the development of any one of the following severe complications during the course of illness: ‘shock’, ‘severe bleeding’, ‘severe fluid leakage’, ‘organ failure’ and/or ‘need for ICU/HDU care’

We recommend measuring each of these outcomes independently and reported separately, rather than as a composite measure.

Need for ICU/HDU care

A patient is classified as having the ‘need for ICU/HDU care’ if they were admitted/transferred to ICU/HDU and/or required one or more of the following life-sustaining interventions* at any point during hospitalisation, regardless of actual ICU/HDU admission status.

*__Interventions__:

Respiratory Support

- Invasive mechanical ventilation
- Non-invasive ventilation (e.g., new requirement for CPAP, BiPAP)
- High-flow oxygen therapy (up to 60 L/min flow rates) (12)

Cardiovascular Support

- Administration of vasopressors or inotropes to manage shock or persistent hypotension

(Patient meets this definition if they exhibit systolic blood pressure (SBP) below the age- and sex-adjusted threshold (SBP < 90 mmHg or MAP < 65 mmHg in adults; age-specific cutoffs for children) and remain hypotensive after receiving an initial IV fluid bolus of ≥ 20 mL/kg (e.g., Ringer's lactate, normal saline) over ≤ 30 minutes.
Persistent hypotension is confirmed when additional fluid boluses (≥ 10 mL/kg per bolus) or continuous IV fluids at ≥ 2 times maintenance rate are required. Patients whose hypotension resolves after a single bolus or those with hypotension due to non-infectious causes (e.g. haemorrhage, cardiogenic shock) are excluded from this definition)

Renal Support

- Initiation of acute dialysis or continuous renal replacement therapy due to kidney failure

Neurological Support

- Reduced consciousness (GCS ≤ 8)
- Seizures requiring intravenous antiseizure medications

Organ failure and severe bleeding

- As per suggested assessment for the relevant outcome

Organ dysfunction

Organ failure is defined as the dysfunction of one or more vital organ system assessed using the modified Sequential Organ Failure Assessment (mSOFA) score, adapted for dengue at least three times, at randomization and between 4 and 8 days from symptom onset. Each organ system component of mSOFA score should be recorded and reported independently to accurately capture the nature and cause of organ failure.

*It is suggested to measure AST and ALT when possible as an exploratory outcome, but it should not be used alone to define liver failure.

Severe bleeding

Severe bleeding is defined as any bleeding event that results in hemodynamic instability, requires blood transfusion, involves a critical organ, or leads to death.

A patient is classified as having severe bleeding if they meet the following criteria:
Either:

5. Bleeding that directly results in death.

OR

6. Symptomatic bleeding in critical areas or organs, such as:
    - Intracranial (e.g., cerebral hemorrhage)

- Intraspinal
- Intraocular (leading to vision impairment)
- Retroperitoneal
- Intra-articular
- Pericardial
- Intramuscular with compartment syndrome

OR

7. Hemodynamic instability presenting as bleeding necessitating medical intervention causing a fall in systolic blood pressure (SBP) below absolute cutoffs:
    - Adults: SBP < 90 mmHg
    - Children <1 year: SBP < 70 mmHg
    - Children 1–10 years: SBP < [70 + (2 × age in years)] mmHg
    - Children >10 years: SBP < 90 mmHg

Or a heart rate >110 beats per minute necessitating medical intervention

AND

8. Bleeding, leading to a decrease in haemoglobin levels of ≥2 g/dL (1.24 mmol/L) or necessitating the transfusion of 2 or more units of whole blood or red cells.

Severe fluid/plasma leakage

We suggest measuring 'severe plasma leakage' defined as a clinically significant and/or measurable loss of intravascular fluid into third spaces, by clinical examination at randomization and every other day between days 4 and 8* AND imaging findings, if possible.

*Severe plasma leakage will be confirmed if at least one of the following independent criteria is met:

Either:

1. Evidence of significant extravascular fluid accumulation on clinical examination (and ideally confirmed by imaging)
    - (New pulmonary pleural effusion or new large volume ascites) causing respiratory compromise

OR

2. Hemoconcentration confirming significant plasma leakage
    - ≥20% increase in hematocrit compared to baseline (if available)

Development of shock

'Development of shock' defined as circulatory failure with inadequate oxygen delivery to tissues, classified into compensated and decompensated shock, and is assessed by measuring objective hemodynamic parameters, including pulse pressure, systolic blood pressure, and clinical signs of hypoperfusion.
A patient is classified as having shock if they meet the following objective hemodynamic markers:

Either:

4. Pulse pressure ≤ 20 mmHg OR Shock Index ≥ 1.0 (Heart Rate / SBP ≥ 1.0 in adults and children >5 years)

OR

5. Systolic Blood Pressure (SBP) below absolute cutoffs:
   - Adults: SBP < 90 mmHg or MAP<60
   - Children <1 year: SBP < 70 mmHg
   - Children 1–10 years: SBP < [70 + (2 × age in years)] mmHg
   - Children >10 years: SBP < 90 mmHg

AND

6. In addition to meeting one of the above criteria, objective evidence of hypoperfusion with at least 1 of the following:

- Peripheral capillary refill time > 2 seconds with a SOP (13, 14)
- Urine output < 0.5 mL/kg/hour for ≥ 6 hours if feasible
- Cold/clammy peripheries
- Agitation or altered mental state

Need for hospitalisation

We recommend measuring 'need for hospitalisation' during the acute illness episode by two separate parameters:
(a) admitted to hospital for any medical reason (for healthcare utilization purposes);
(b) developed one or more warning signs proposed by the WHO, regardless of actual hospitalisation status.

Viral load outcome

At the current stage there are no feasible measurement instruments to recommend measurement in every single clinical trial.
If feasible and resources allow, we recommend measuring viral load as the quantification of dengue virus RNA in blood, by real-time quantitative PCR (qPCR) before randomisation, at 24 and 48 hours.

We recommend reporting individual viral load measurements separately, in addition to change in viral load over time and area under the viremia curve. Viral load data should always be reported alongside day of illness.

5. Online meeting 5 Feb 2025. Participants.

Country of residence	Study team members	Representatives of other dengue stakeholders	Healthcare professionals and/or researchers treating/studying dengue
Brazil			2
Colombia			1
Cyprus	1		1
Malaysia			1
Singapore			2
Switzerland		1	1
UK	2		2
USA	1	1	3
Vietnam			2
Total	4	2	14

6. Hybrid meeting 24 Feb 2025. Participants.

Meeting participants	On site	Online	Voting
Study team members	4	3	0
Representatives of other dengue stakeholders	7	2	0
Healthcare professionals/Researchers	26	5	29
Total	36	10	29

Country of residence	Study team members	Representatives of other dengue stakeholders	Healthcare professionals and/or researchers treating/studying dengue
Brazil			2
China		1	
Colombia			3
Cyprus	1		
India			1
Malaysia			4
Russia	1		
Singapore			1
Sri Lanka			1
Switzerland		3	1
Taiwan	1		
Thailand			2
UK	3		3
USA		5	4
Vietnam	1		9
Total	7	9	31

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