**A national consensus management pathway for Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS): The results of a national Delphi process**

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**Competing Interests:**

All authors have completed the ICMJE uniform disclosure form at ww.icmje.org/coi\_disclosure.pdf.

**Data sharing:**

Relevant raw data will be provided in supplementary material. No further data will be available for sharing.

**Transparency statement**

The lead author (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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**Author Contributions**

RH and BA designed and conducted the study with SK with additional input from SNF, CEJ, MK and RA. RH and BA wrote the paper with detailed input from SK, MK, SNF and CEJ. All authors were involved in study analysis and approved the final manuscript.

**Patient and Public Involvement**

There was no involvement of patients or their families in this management pathway. We recognise their important role in the care of children with PIMS-TS and intend to consult them for future iterations of the pathway.

**Key Messages**

* **PIMS-TS is a novel condition which has emerged during the COVID-19 pandemic and ongoing research into its cause, the disease course and therapies which improve the outcomes of children with PIMS-TS is essential and should be supported by recruitment to relevant studies including RECOVERY, ISARIC/CCP-UK, DIAMONDS and BPSU surveillance in the UK.**
* **Children suspected of having PIMS-TS should undergo first line blood tests to determine if they meet the diagnostic criteria. Subsequent tests to determine the severity of disease, exclude important differential diagnoses and screen for cardiac involvement are recommended.**
* **The multi-disciplinary team (MDT) is an essential facet in the care of children with PIMS-TS and every child with suspected PIMS-TS should be discussed by an MDT within 24 hours of suspicion of the diagnosis and when considering biological therapy.**
* **Therapeutic choices for PIMS-TS are dependent on the presenting phenotype (Kawasaki-like disease or non-specific presentation) and high-risk features or the severity of disease. A step-wise pathway of IVIg, followed by methylprednisolone and biological agent is recommended for children not recruited to a trial.**
* **This management pathway is based primarily on expert opinion and should be updated as new evidence emerges.**

**Summary**

Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS) is a novel condition which has arisen in the past 5 months. We aimed to develop a national consensus management pathway to provide guidance for clinicians caring for children with PIMS-TS. A three-phase online Delphi process and virtual consensus meeting sought consensus over the investigation, management and research priorities from 72 multidisciplinary participants, 46 of whom completed the process, caring for children with PIMS-TS. 140 consensus statements were used to derive the consensus management pathway which describes the initial investigation of children with suspected PIMS-TS including blood markers to help to determine the severity of disease, echocardiogram, ECG and a viral and septic screen to exclude other infectious causes of illness. The importance of the multidisciplinary team in decision-making for children with PIMS-TS is highlighted throughout the guidance, along with the recommended treatment options including supportive care, IV Immunoglobulin, methylprednisolone and biological agents for children with Kawasaki-like disease and non-specific presentations.

This national consensus pathway has been developed for children suspected of having the novel syndrome PIMS-TS in a timely, cost-efficient manner, in the midst of a global pandemic. Use of a rapid online Delphi process has made this consensus process possible. Future evidence will inform updates to this guidance, which in the interim provides a solid framework to support clinicians caring for children with PIMS-TS. The study has directly informed new PIMS-TS specific arms for children as part of the adaptive UK RECOVERY trial protocol which is the first formal randomised controlled trial of therapies in PIMS-TS globally.

**Introduction**

Since the first reports from London, UK, in late April 2020, many countries globally have reported children presenting severely unwell with features of significant inflammation temporally related to the COVID-19 pandemic. These include the United States of America(1), France(2, 3), Italy(4) and the United Kingdom(5, 6). Subsequently, parallels have been drawn between the presenting features of this syndrome and other known conditions, including complete, incomplete and atypical Kawasaki Disease (with or without coronary artery dilatation), toxic shock syndrome, viral sepsis and less commonly, Macrophage Activation Syndrome (MAS) or Haemophagocytic Lymphohistiocytosis (HLH). Preliminary case definitions of this novel inflammatory condition have been published by the Royal College of Paediatrics and Child Health (RCPCH)(7), the Centre for Disease Control(8) and the World Health Organisation(9). As these definitions are based on relatively small numbers of children seen, variation exists. For the purposes of this paper, which focuses on the opinions of UK clinicians, the RCPCH definition, which names the condition ‘*Paediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS)’* has been used.

It rapidly became apparent that there are many clinical uncertainties regarding this new disease syndrome. These include the prevalence, apparent differing clinical phenotypes, variable severity, the clinical course, and optimal management. To provide clarity to UK clinicians, NHS England led a process to develop national clinical management guidance through a rapid consensus exercise. The process also explored where equipoise exists for the planning of formal research trials including children with PIMS-TS. Given the status of PIMS-TS as a new syndrome, clinical consensus combined with experience in treating the initial cases was the starting point in the process of constructing a clinical guideline and defining key areas of research. The UK Randomised Evaluation of COVID-19 (RECOVERY) trial (<https://www.recoverytrial.net/>) steering committee made the trial protocol (including anti-inflammatory agents) available to children with COVID-19 and related inflammation prior to NHS England initiating the consensus process. Therefore, enrolment to the RECOVERY trial, and future studies, were included within the scope of the consensus process.

A Delphi process is a well-established method for achieving consensus from multiple groups of stakeholders(10), and has been used within healthcare for multiple reasons, including development of core outcome sets and identification of metrics for monitoring quality of care (11-15). Broadly, a Delphi process involves asking respondents to complete sequential questionnaires with group opinion fed-back to individual participants in between completion of the questionnaires. Children with PIMS-TS require the expertise of clinicians who specialise in immunology, infectious diseases, respiratory, rheumatology, cardiology, intensive care, general paediatrics, haematology and in some cases surgery, radiology and neurology. The aims of this study were therefore to seek consensus from participants within these key stakeholder groups regarding the diagnosis and management of children with suspected PIMS-TS, to identify areas where equipoise existed in order to inform subsequent research, and to explore whether consensus existed with regards to how children with PIMS-TS could be enrolled in the RECOVERY trial.

**Methods**

In summary, a three-phase online Delphi process was used to identify statements where a national multidisciplinary panel agreed that consensus existed regarding the investigation and management of children with suspected PIMS-TS (Supplementary Information 1). A consensus meeting was conducted via a web-based platform to review statements where consensus had not been achieved during the Delphi process. A face to face consensus meeting was not conducted due to COVID-19 social distancing restrictions.

This work was considered quality improvement by the Health Research Authority, and therefore approval by an ethics review board was not required.

The consensus processes centred on the definition of PIMS-TS, published by the RCPCH, which is as follows:

1. *A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features. This may include children fulfilling full or incomplete criteria for Kawasaki Disease.*
2. *Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus.*
3. *Positive or negative SARS-CoV-2 PCR*

Clinicians were purposively selected to cover the range of multidisciplinary clinical and research expertise needed to diagnose and manage children with PIMS-TS, and were invited personally, by email or by telephone to participate in the study through sub-speciality groups and personal contacts. Clinicians were selected due to their expertise within their respective fields, their clinical experience of caring for children with PIMS-TS or their involvement in research into PIMS-TS. Those who agreed to participate were divided into three panels in order to facilitate feedback throughout the Delphi process:

1. Paediatric Infectious Diseases and Immunology, Paediatric Rheumatology, Paediatric Respiratory, Pharmacist with specialist expertise in biological therapy
2. Paediatric Cardiology, Paediatric Intensive Care and Transport, Paediatric Haematology
3. General Paediatricians, Paediatric Radiologists and Paediatric Surgeons.

Representation in all three panels was sought, but experience in management of children with PIMS-TS, and the need to rapidly conclude the consensus process were prioritised over seeking wider engagement of clinicians or achieving numerical balance between the panels.

Whilst in most healthcare related Delphi processes it has been appropriate to involve patients or the public as key stakeholders, it was felt that the clinical expertise required to assess the statements around which consensus was required for development of this clinical management pathway precluded inclusion of these groups. Patients and the public were therefore not involved in either the design or conduct of this study.

Statements for assessment in phase one of the Delphi process were derived by the study management group from reviews of the existing literature and expert opinion, including draft local guidelines. Participants in the Delphi process were asked in phase one and phase two to propose additional statements which they considered necessary for assessment. These were reviewed by the study management group, and if falling within the scope of the study, were included for assessment in the subsequent phase.

A three-phase online Delphi process was conducted concurrently for the three panels. Results of the Delphi process were discussed in a virtual, online, consensus meeting attended by a representative sample of experts from each panel. The consensus meeting was chaired by an independent, non-voting, non-paediatric clinical academic experienced in Delphi methodology.

In phase one of the Delphi process, participants were asked to score statements from 1-9 based on how much they agreed with the statement. Scores of 1, 2 and 3 were ‘disagree with statement’, 4, 5 and 6 were ‘agree with statement’ and 7, 8 and 9 were ‘strongly agree with statement. Participants were asked to score a statement ‘don’t know’ if they did not consider themselves to have expertise in that area. In phase two, participants were shown graphical and numerical representations of how their panel overall had scored each statement and were asked to re-score the statements taking that information into account. Some statements were re-worded or were clarified with additional words in-between phase 1 and 2 in response to respondent’s comments. In phase three, participants were shown graphical and numerical representations of how all three panels had scored each statement and asked to re-score the statements taking that information into account.

Participants were sent a reminder email if they had not completed the phase with 24 hours remaining. Participants who did not complete a phase were deemed to have withdrawn from the study and were not invited to take part in subsequent phases.

The established COMET methodology for determining consensus was used(16). ‘Consensus agreement’ was defined as ≥70% of participants scoring a statement 7-9 (strongly agree), and <15% of participants scoring a statement 1-3 (disagree) in all three individual panels. ‘Consensus disagreement’ was defined as ≥70% of participants scoring a statement 1-3, and <15% of participants scoring a statement 7-9 in all three individual panels. Following phases two and three, if statements met ‘consensus agreement’ or ‘consensus disagreement’, they were excluded from the next stage of assessment.

Statements where consensus had been achieved in two out of three panels at the end of phase three were discussed in the consensus meeting. Statements discussed at the consensus meeting were assessed using a simple binary vote of ‘agree’ or ‘disagree’. Those statements where more than 70% of participants either agreed or disagreed with the statement were deemed to have met consensus. If consensus was not met following the initial vote, in depth discussions were held to understand why disagreement existed and were followed up with a second vote. Where participants felt agreement could be achieved with minor modifications to the statements, these modifications were made. The final guidance is formed from those statements which met ‘consensus agreement’ or ‘consensus disagreement’ after phase two, phase three, or the consensus meeting.

The consensus statements are applicable to children in the UK suspected of having PIMS-TS. They may also be applicable in other high-income countries, although the views described only represent those of UK clinicians. They are less likely to be applicable in countries where infrastructure and access to healthcare and treatments are significantly different to that of the UK.

**Findings**

A total of 98 participants were invited to contribute to the Delphi process, 72 agreed and completed phase 1, 46 (64%) completed all three phases (Table 1). Throughout the Delphi process the full range of specialities were represented apart from haematology where no participants continued to phase 3 (Supplementary Results). Ten participants attended the consensus meeting (Table 1). The flow of statements through the consensus process is shown in Figure 1.

**Table 1: Participants**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Panel | Completed phase 1  n (% of invited) | Completed phase 2  n (% of invited) | Completed phase 3  n (% of invited) | Attended consensus meeting  n (% of invited) |
| Panel 1 | 40 (78%) | 32 (80%) | 25 (78%) | 3 (43%) |
| Panel 2 | 17 (77%) | 11 (65%) | 11 (100%) | 4 (80%) |
| Panel 3 | 15 (60%) | 13 (87%) | 10 (77%) | 2 (40%) |
| Total | 72 (73%) | 56 (78%) | 46 (82%) | 10 (59%) |

*Panel 1 (IDI): Paediatric Infectious Diseases and Immunology, Paediatric Rheumatology, Paediatric Respiratory, Pharmacist with specialist expertise in biological therapy;*

*Panel 2 (ICU): Paediatric Cardiology, Paediatric Intensive Care and Transport, Paediatric Haematology;*

*Panel 3 (PAE): General Paediatricians, Paediatric Radiologists and Paediatric Surgeons.*

217 statements were assessed in phase one, 35 statements were added for assessment in phase two, and 3 statements added for assessment in phase three. Supplementary material 1 describes the detailed consensus process and lists all assessed statements and their final consensus decisions determined either in Phase 2 or Phase 3. The final guidance is formed from the 140 statements where consensus agreement was achieved throughout the consensus process (Figure 1).

**Consensus Statements**

Figures 2, 3 and 4 display the full consensus guidance and integration with clinical research developed from this process. Investigation of children suspected of having PIMS-TS is recommended to take place making use of a clinical multidisciplinary team and step-wise clinical management. To diagnose PIMS-TS, the first step after clinical history and examination is to obtain blood tests, specifically full blood count, C-reactive protein, urea, creatinine and electrolytes and liver function tests. If these support a diagnosis of PIMS-TS then additional investigations, described in box 1b are recommended to determine the diagnosis and the severity of disease and look for complications of PIMS-TS.

The consensus process determined that patients with PIMS-TS should be primarily categorised according to the phenotype of disease (‘Kawasaki-like disease’ or ‘Non-Specific’) but that severity assessment for both phenotypes is recommended to support clinicians in determining a patient’s location of care. Kawasaki-like disease is defined using the criteria for the diagnosis of Kawasaki Disease published by the American Heart Association(17) and it is recognised that the distinction of phenotypes is based on expert opinion, rather than a proven biological difference. The consensus process did not determine that children with shock on presentation should be cared for in a level 2/3 unit with availability of ECMO on site. However, there was significant discrepancy between the views of the intensive care panel (who felt the ability to deliver ECMO is important) and the clinical infectious diseases and immunology panel, where most agreed that ECMO availability was not necessary. This may be due to many centres with infectious diseases and immunology doctors not being co-located with ECMO services and displays the importance of the input of the multi-disciplinary team (MDT) in the management of children with PIMS-TS. Figure 3 describes the core and additional members of the MDT and that all children with PIMS-TS should be discussed by an MDT within 24 hours of admission.

All children with PIMS-TS should be treated for presumed sepsis until the microbiological cultures results are available. The Delphi process has provided the consensus for the adaptation of the UK RECOVERY randomised controlled platform trial (www.recoverytrial.net) to open specific arms for children with PIMS-TS for all phenotypes and it is recommended that all children who meet the criteria to be included in the trial are offered the opportunity to do so. Out-with the RECOVERY trial, specific management varies according to phenotype. IVIg is recommended for all children with Kawasaki-like Disease but is not recommended for each and every child with a non-specific presentation, for whom no treatment may be required. Methylprednisolone is recommended as the second-line therapy for both phenotypes and is advised to be given at the same time as IVIg for ‘high-risk’ children with Kawasaki-like Disease. The dose of methylprednisolone was not asked about in the Delphi process, but dosing of 10-30mg/kg/day for 3 days is typically recommended. Biological therapy is recommended as the third-line therapy for all children with PIMS-TS. There was consensus that infliximab is the biological agent of choice for Kawasaki-like Disease but there was equipoise between anakinra, infliximab and tocilizumab for children with a non-specific presentations of PIMS-TS.

Consensus was gained in the consensus meeting for children with both phenotypes of PIMS-TS to receive either IVIg or methylprednisolone as a first line therapy in a clinical trial setting and this has been incorporated into the first stage randomisation of the RECOVERY trial. If an MDT decision has been made to commence biological therapy there was consensus that a child within the RECOVERY trial should be offered the opportunity to enter the second stage randomisation of tocilizumab or standard care.

Consensus was achieved to follow local protocols for anti-platelet therapy for children with Kawasaki-like Disease and that all children with PIMS-TS should be given low-dose aspirin for a minimum of 6 weeks. There was agreement that, for a child who is otherwise well, stable cardiac function and no pyrexia for 24 hours are criteria for discharge.

Clinical follow-up is recommended at 1-2 weeks and 6 weeks after discharge with echocardiography being a key investigation during follow-up as coronary artery aneurysms have been seen even after mild disease courses(5). Multi-disciplinary follow-up with Paediatric Infectious Diseases and Immunology consultants and Paediatric Cardiologists is recommended for children with coronary artery abnormalities or who have required organ support for PIMS-TS.

There was strong support for ongoing research into PIMS-TS and consensus that children should be offered the opportunity to be included in studies including DIAMONDS, ISARIC/CCP-UK and the national BPSU PIMS-TS registry.

**Discussion**

Use of an online Delphi process and virtual consensus meeting has enabled a National multidisciplinary panel to achieve consensus around 140 statements relating to the investigation and management of children with PIMS-TS, and participation of these children in studies including, but not limited to, DIAMONDS (<https://www.diamonds2020.eu>), ISARIC CCP-UK (<https://isaric4c.net>) and the RECOVERY trial (https://www.recoverytrial.net). Based upon the results of this process, it has been possible to develop a national consensus management pathway for the care of children with suspected PIMS-TS within 6 weeks of the need for such guidance becoming apparent. However, all participants recognise that this process has relied on clinical opinion based upon the limited evidence currently available. Until further evidence materialises, this management pathway can provide a framework for managing children with suspected PIMS-TS.

The key strength of this work was the ability to achieve consensus relating to the management of a novel, complex condition, based upon quantitative data, from a relatively large number of participants, spread across multiple geographic regions. It was conducted in a short period of time, in the middle of a global pandemic, without the ability to conduct face to face meetings, large round table discussions, or focus groups. A similar process has been used in the United States of America for Multisystem Inflammatory Syndrome in Children (MIS-C)(18). However, the small number of participants and less diverse range of experts limit the applicability of some of the findings, particularly around the choice of second line biological agent where the equipoise that is found within the Delphi process described in this manuscript is not shown.

There are three key limitations to this study. Firstly, the output and recommendations from a Delphi process can only ever be as robust as the statements that are assessed within it. As the statements assessed here were all developed based-upon level five evidence (expert opinion), the guidance can only ever seek to summarise this expert opinion. Once higher levels of evidence become available, and increased clinical experience is developed, this evidence and experience should be incorporated into future guidance in order to ensure that the management pathway remains relevant and up to date. Given the cost-efficient, timely nature of the conducted Delphi process, it would be feasible to re-run the process when significant new data comes to light, and to use the results of the process to inform development of guidance. The second limitation of the study is that a smaller number of participants were recruited from stakeholder groups than would normally be aimed for in conduct of a Delphi process, and the scope of the work precluded inclusion of parents, young people and/or members of the public in the process. Despite this, adequate representation was achieved across all panels, with multiple representatives from each stakeholder group participating. However, had time, and the need to ensure clinical expertise of participants not been such pressing factors, it would have been preferable to seek opinions from a larger number of stakeholders, and from parents, young people and the public. Thirdly, the consensus meeting included only a few representatives of each stakeholder group due to the online format and need to ensure opinions from all stakeholder groups during the meeting.

The management pathway created from this consensus process aligns well with the evidence base which currently exists for PIMS-TS(5, 19, 20). It builds on the RCPCH PIMS-TS definition(7), which was developed with a much smaller working group and provided principles for management based on the experience of managing the first cases of PIMS-TS in the UK, the majority of which were children with more severe presentations of PIMS-TS. There is increasing awareness that there is a spectrum of severity in patients with PIMS-TS and it is acknowledged that clinicians should consider a wide-differential diagnosis in those patients presenting with persistent fever and evidence of inflammation, but without the other features of PIMS-TS that have been described. This management pathway is based on consensus from a wide group of clinicians and provides granular, practical guidance for the management of children with PIMS-TS. Consensus was reached that phenotype should be the primary method of classifying children with PIMS-TS. The guidance focuses on the recognition of markers of severe disease and in particular cardiac disease which has been described in both phenotypes of PIMS-TS(3, 5). It includes a management pathway for Kawasaki-like Disease which aligns with current guidance for the management of Kawasaki Disease(17), and may help to address the current variation in treatment which is occurring regarding the indications for intravenous immunoglobulin (IVIg) and steroids(3, 20, 21). Indicators of ‘high risk’ disease are extrapolated from the current understating of Kawasaki Disease and PIMS-TS but vigilance for cardiac complications of PIMS-TS is recommended for all children, regardless of the assessment of severity of disease. Discussion and voting during the consensus meeting found equipoise for randomising within trials between IVIg and Methylprednisolone for both phenotypes of PIMS-TS. There was support within the consensus group that it would be appropriate for a trial to consider ‘supportive care only’ as an additional arm, but this was not voted on and therefore not included in the consensus guidance. The distinction between phenotypes and treatment strategies is based on expert opinion as the biological mechanisms for PIMS-TS have not yet been elucidated. For this reason, after discussion at the consensus meeting, it was determined that equipoise exists between methylprednisolone and IVIg as a first-line therapy for both phenotypes of PIMS-TS. This has important implications internationally as there is a limited supply of IVIg but methylprednisolone is readily and cheaply available.

Within the Delphi process, significant discrepancy was noted between panel one (paediatric medical specialists with training in immunology and infectious diseases) and panel two (paediatric intensivists, cardiologists and haematologists) with regards to whether children with PIMS-TS should be cared for in units with extra-corporeal membrane oxygenation (ECMO) availability. 90% of panel two strongly agreed this should be the case, whilst 86% of panel one disagreed. Data collected by the British Paediatric Surveillance Unit (<https://www.rcpch.ac.uk/work-we-do/bpsu>) PIMS-TS surveillance study will help to provide the underpinning research to resolve this discrepancy. Until such data are available, we would reinforce the need for significant clinical decisions relating to the management of children with PIMS-TS to be taken within a multi-disciplinary setting, with adequate representation from all core members of the multidisciplinary team. Other areas where the need for future research have been highlighted by this Delphi process include the indications for, and identification of, the most appropriate immunomodulatory therapy for use in children with the non-specific PIMS-TS phenotype, and whether IVIg or methylprednisolone should be first line therapy for children with both phenotypes of PIMS-TS.

As a direct result of this study, the RECOVERY trial (www.recoverytrial.net) has been amended (protocol v8.0, opening August 2020) to allow paediatric clinicians to select treatment arms to compare high dose steroids (methylprednisolone) versus no additional treatment (in the presence and absence of intravenous immunoglobulin, IVIg) and IVIg versus no additional treatment (in the presence and absence of high dose steroids) for the initial treatment of PIMS-TS(22). This pragmatic design allows investigators to use no treatment, IVIg or high dose steroids as standard care if deemed necessary. It allows the effects of high dose steroids and IVIg to be compared with no additional treatment separately (in presence and absence of other drugs), and it allows children with a wide spectrum of severity to be recruited. By using this Delphi study to inform the trial design, it is hoped that this will maximise clinicians’ willingness to recruit to the clinical trial. This is a critical clinical trial in the context of a global pandemic, due to the high cost and poor availability of intravenous immunoglobulin supply in the UK and worldwide.

This consensus management pathway relating to the treatment of children with PIMS-TS is based on consensus expert opinion and is intended to act as a framework for the safe management of children with this condition. As new, higher level evidence become available, the guidance will be updated.

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