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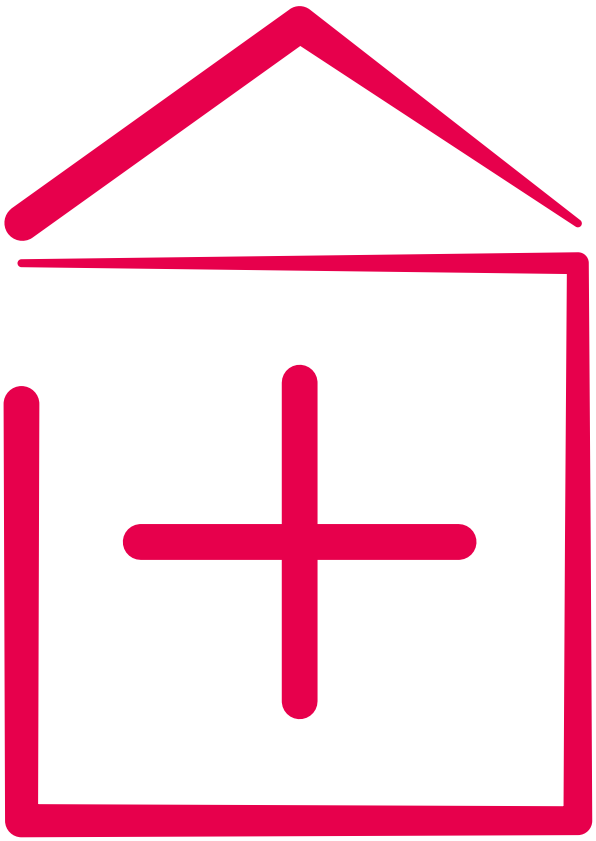
Academy of Medical Royal Colleges

Stakeholder consultation comments & responses to the Academy Sepsis position statement



For any further comments or clarifications, please contact Julian Bion: J.F.Bion@bham.ac.uk

Executive summary		
Organisation	**Comments**	**Page and para / response**
Defence Medical Services	The Defence Medical Services holds a very similar view to that expressed in the guidance.	Thank you.
Royal College of Physicians	The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our representative, and our Clinical Director for Quality improvement and Patient Safety and would like to comment as below. Thank you for the considerable work that has resulted in this excellent evidence review and guidance. We recognise that our feedback from the previous versions has been considered and influenced this version. Indeed, many of our points have been covered by changes in the main body of the report. However there some elements of this that seem to be importantly different in the executive summary. Our main concern remains the importance of clinical assessment and judgement being complemented by NEWS2 rather than NEWS2 being the determinant of speed of response. This is addressed in the narrative in the full report but not fully replicated in the executive summary. RCP are very clear in our guidance on NEWS 2 that *The NEWS should be used as an aid to clinical assessment – it is not a substitute for competent clinical judgement. Any concern about a patient's clinical condition should prompt an urgent clinical review, irrespective of the NEWS.*	Thank you. We have added this text to para 2.6.1: "*At all stages the NEWS-2 should be used as an aid to clinical assessment, not a substitute for competent clinical judgement. Any concern about a patient's clinical condition should prompt an urgent clinical review, irrespective of the NEWS-2.*"
	Section 2.1.1 states *This report proposes that urgency of treatment of adult and paediatric patients with suspected sepsis is* ***based on National Early Warning Scores (NEWS-2 or PEWS) combined with clinical and laboratory assessments of probability of infection****. A structured approach is presented in the form of clinical decision support frameworks linking timeframes for initial assessment and treatment to severity bands.* We recommend this wording is changed to ***based on National Early Warning Scores (NEWS-2 or PEWS) combined with clinical and laboratory assessments of severity, urgency and probability of infection***	Thank you. We have added these sections of text.

	Section 2.6.1 states *The working group unanimously agreed with the principle that treatment urgency for adults and children should initially be determined by severity of illness using NEWS-2 or PEWS, respectively.* We recommend the wording is changed to *using NEWS-2 or PEWS, respectively* ***as part of clinical assessment***	
Intensive Care Society	Seems fair enough and clear with good intentions Seems fair enough. Clear intentions. Personally, I'd prefer more snappy dialogue in all of this document with very clear recommendations and the background details reserved for further reading (say after the key recommendations and tables). You don't get to the coloured guideline table until page 29 which seems a long way down.	Thank you. It is our intention to produce a succinct summary of the report for peer-reviewed publication.
Northern Ireland Intensive Care Society	The executive summary is clearly written and addresses the need to stop and ascertain the reason for organ dysfunction rather than focus on antibiotic administration. Should there be a statement on source identification and control? This is appropriately discussed further in the document.	We have added: '*Antimicrobial treatment must be accompanied by source identification and control and antimicrobial stewardship.*'
Royal College of Physicians of Edinburgh	College Fellows have commented that this is an informative and very helpful document. The College requests that one additional point be made in the statement, which is around awareness and education: that the term "sepsis" is not synonymous with "infection". Unfortunately the two are frequently employed interchangeably such as in "urosepsis" when a patient has a simple UTI, "septic arthritis" when a patient has an infected joint and "neutropenic sepsis" when the patient has neutropenia but may actually have no evidence of infection.	We have added to 1.6 the phrase in bold: *In both adults and children, the propensity of physicians to prescribe antibiotics is increased by diagnostic uncertainty,* ***by assuming equivalence between infection and sepsis****, and by performance targets which prioritise potentially unnecessary prescribing over antimicrobial stewardship.* We also explicitly address this issue in para 6.8.
NHS England and Improvement AMR Programme, including collated comments from the Acute Deterioration Board.	Well written and concise, has all the information required. No other comments.	Thank you, and additional factors addressed below
	We welcome a more nuanced and evidence-based approach to management of sepsis and the positive impact adoption of this position statement will have on antimicrobial stewardship.	
	The core proposal provides a clear framework for adult and paediatric teams working with patients presenting with confirmed or possible Sepsis. However, there are several key factors that it will be important to take into account in developing the final version of the framework.	

NHS England and Improvement Professional & System Leadership - Community Nursing	Informative, well written - with our comments being submitted after the initial document consultation and amendments. Agree with comment from DHSC need to review if there are any gaps out of hospital in relation to awareness / identification of sepsis. Also to highlight the importance of sepsis awareness, education, escalation in community nursing where people often live on their own and may not be seen by anyone until the following day.	Thank you. It seems very likely that there will be gaps in awareness outside hospital, as there are inside. Our proposal for audit and research will help to close those gaps. Education certinaly important. We state in 6.1.1: : educational and clinical support interventions can empower clinicians to make more nuanced judgements [May 2021] [Ouldali 2017].
UKCPA Critical Care Group	Clear and well presented, if slightly long.	We plan a shorter version for peer-reviewed publication.
UK Clinical Pharmacy Association (UKCPA) Infection Committee	Latest ESPAUR document shows that hospital antibiotics have dropped in 2020-2021.	P4 1.5; Also p14 10.2 We have now included the recently-published ESPAUR report for 2020-2021 but use the previous report for examination of trends to avoid the impact of the pandemic.
UK Sepsis Trust	*The evolution of clinical guidelines into performance metrics with penalties for non-compliance has inhibited the exercise of clinical judgement, distracted from making a non-infective diagnosis and hampered antimicrobial stewardship, contributing to increasing antimicrobial resistance.* We find this statement suggestive of a causal relationship between performance incentivization and increasing AMR, which is not evidenced in this paper or in the literature. We suggest that there is a risk that this statement might be misinterpreted.	1.1 We provide some circumstantial evidence in the manuscript, but accept that this perspective is based on the views of frontline staff rather than a formal study. We have softened this statement by using the modal form ['may have']
	It is estimated that there are in the region of 47,000 'suspected sepsis' adult admissions for England, with a mortality of 7.2%. This is factually incorrect, and indeed is a claim which we believe doesn't stand up to even basic scrutiny. See comment with full explanation on section 6.1 below.	1.4 Responded to in more detail below. Thank you for having identified this error.
	In the UK, prescription of antimicrobials has diminished in the community since 2015, but has increased in hospital, particularly broad-	1.5 Modified to *'which could be a consequence of'*.

	spectrum agents, related in part to exhortations to administer these drugs within one hour of presentation of presumed sepsis. The authors offer no evidence to back the claim of a causal relationship between 'exhortations' to administer rapid antimicrobials and an increase in antimicrobial prescription. Could this be more carefully worded?	
	This framework provides an optimal balance between patient safety and antimicrobial stewardship, while allowing clinicians to exercise judgement in the care of individual patients. We find this a rather bold claim!	1.11 Revised to '*This framework aims to provide a balance...*' We also recommend research evaluation.
United Kingdom Health Security Agency	Thank you for the inclusion of paediatric population in the position statement, this is much appreciated. The addition of a section on neonatal sepsis, a top global killer and a condition responsible for long-term changes in microbiota early in life, would be welcome.	Neonatal sepsis is indeed a most important topic, but not one which we feel we can include here. It deserves a separate review. We have now mentioned neonates under 'limitations' towards the end of the report and referenced NICE guidance. Inclusion of neonates would necessitate a whole new section, as neonates can be managed in Neonatal Units/ICUs [inborn] or after discharge from hospital when they present to a children's hospital/ED/Unit. The management and approach is very different,and neonates are not usually included in sepsis guidelines for children.
	Agree regarding children, however for neonates and very young infants this might be higher?	
West Midlands Adult Critical Care Network	'...based on NEWS-2 or PEWS bands of 0, 1-4, 5-6, and ≥7, and PEWS bands of 0, 1-4, 5-8, and ≥9,..' Some confusion here – as PEWS seems to contribute to two different sets of bands. Is the first mention necessary and/or correct?	1.9 Thank you for having identified this editorial malfunction. The range bands are now harmonised and are aligned with the SPOT programme, with the exception that our top PEWS band is >9, and combines the elements of >13 in SPOT.
Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection [APRHAI]	Very supportive of this initiative and agree with the underlying impression that patients are now getting antibiotics in the ED that they may not need.	Thank you.
	The work appears to be very comprehensive and the outcomes of it are appealing to anyone who has harboured or expressed concerns about the impact of approaches to	

	'sepsis' that increase the risk of inappropriate broad spectrum antimicrobial use.	
	This seems an appropriate approach to balance the imperative of early treatment against the risks of overtreatment and antimicrobial stewardship	
National Outreach Forum	Please can we use British spellings – cognisant rather than cognizant for example	1.1, P3 Done
	The National Outreach Forum would have been very keen to be formally involved in this. Sepsis forms a significant proportion of Critical Care Outreach work and we would have expertise to contribute.	1.3, P3 You do indeed have valuable expertise. That is why we have asked you to contribute formally as one of the stakeholders.
Royal College of Nursing (RCN)	Suggest removing 'physicians' to reflect wide range of medical and non-medical prescribers across the systems. Clinician is a more inclusive term.	1.6, p4 We have used 'clinician' quite widely for that reason. There are some roles where doctors will specifically need to be involved so we have used physician at those points intentionally.
	This sentence needs further clarification: "If additional concerns are identified at this stage, the clinician can 'upgrade' the patient's status to the next severity band". The NEWS2 scores are based on objective measurement of observation.	1.9, P4 Rephrased as: *'…the clinician can 'upgrade' the actions required to those of the next severity band*'.
	Importance of blood culture needs to be emphasised here.	At the end of 1.10 we have added: '*Antimicrobial treatment must be accompanied by source identification and control and antimicrobial stewardship*'. Source identification includes blood cultures.
	Consider Synthesis and recommendations section on a box/table so it is visible when reading the document.	We will produce a shorter abstract once the report is finalised. In the meantime we have added an 'overview' statement to the Executive Summary: '*This report proposes that urgency of treatment of adult and paediatric patients with suspected sepsis is based on National Early Warning Scores (NEWS-2 or PEWS) combined with clinical and laboratory assessments of probability of infection. A structured approach is presented using clinical decision support frameworks.'*

Paediatric Critical Care Society (PCCS)	Overall: PCCS Council thinks this is an excellent document: well written, considered, nuanced, and balanced. It supports its recommendations.	Thank you.
	General: These recommendations are supposed to be UK wide. At present the word 'England' appears 58 times, "Wales' 9 times, Scotland' once, and Northern Ireland 0 times. Some recommendations appear English-centric. For example, section 27.1 refers to PEWS which is an English-based score while Scotland has its own bespoke system. Some deliberate mention of engagement with representatives from all 4 nations might support the paper's legitimacy as a UK-wide document.	We invited representation from the health services of all devolved administrations. Only Scotland participated. Neither Wales nor NI responded to repeated requests despite having active emails. We have continued to share the development of the document with them nevertheless. The Academy permits UK-wide professional engagement. Where we refer to health services data, we are inevitably frequently confined to national data sets, much as we would like a consistent UK-wide system. We do not have data on which thresholds to use for the Scottish PEWS, but would welcome any suggestions. There is no PEWS score specifically for Wales or Northern Ireland, to the best of our knowledge.
System wide Paediatric Observation Tracking (SPOT) programme	The System wide Paediatric Observation Tracking (SPOT) programme welcome the AoMRCs Sepsis paper which will certainly improve the current processes used to assess, detect and respond to children and young people with sepsis, and potential sepsis.	Thank you.
Department of Health and Social Care	This is a well thought out and timely piece of work demonstrating a clear solution to concerns relating to early and, in some cases, misguided use of antimicrobials. It is viewed that a more nuanced approach, which accounts for circumstance, clinical judgement and expertise, would be preferable and that is reflected well in the framework provided in this paper.	Thank you.
	It would be helpful to understand how the proposed framework could be managed and implemented in relation to the wider patient pathway and different healthcare settings (incl. pre-hospital/community health settings).	We have tried to address these points during the subsequent parts of the report.

	NICE, in the context of guidance for the management of COVID-19 pneumonia in a primary care setting states that *'although the NEWS2 tool is not validated for predicting the risk of clinical deterioration in prehospital settings, it may be a helpful adjunct to clinical judgement in adults.* Could it be considered whether there is a gap in terms of prehospital settings for awareness and recognition of detection of sepsis, and if so, whether any gap could be addressed through development of this proposal and its implementation?	
	Feedback from stakeholders reaffirms the perception that current national guidance could be modified to provide better support for clinicians and provide space for them to use their own clinical judgement in the use of antimicrobials.	1.1 We agree!
	Different uses of definitions for sepsis in clinical practice are commonplace. It would be beneficial if any new framework was implemented with a clearly defined and consistent definition for sepsis, that includes nuances for differing circumstances and severity. Could consistent terms for sepsis and septic shock be suggested through this paper? Do we also need to consider defining our language more generally including our terms/definitions for antimicrobials, antimicrobial resistance, and stewardship?	We will provide a taxonomy of sepsis and include this in the Appendix.
	The latest figures on Covid-19 impact on antimicrobial usage in secondary care could be added to illustrate recent changes and the expectation that antimicrobial use will return to pre-pandemic levels – demonstrating why a review of the one hour framework is even more timely for maintaining good stewardship. ESPAUR recently published their latest figures for 2020-2021.	1.5 We have included the graph of antimicrobial use from the ESPAUR 2020-2021 report, in the Appendix.
	Information could be provided about how the new framework would be evaluated and what the iterations process would involve.	1.11 Addressed in para 30.3.
Scottish Anti-microbial prescribing Group (SAPG)	"In general the document was well received and supported – particularly the nuanced approach towards management based on NEWS 2 and likelihood of infection. There will be practicalities regarding infection specialist input during the empiric phase of therapy and some compromise to this has been suggested based on clinical uncertainty and severity of infection."	Thank you

	There is no reference to COVID-19 in the document. This is important as Sepsis and severe COVID-19 may be confused and diagnosis of sepsis may be challenging in the context of COVID-19.	Severe COVID-19 disease actually fulfils the criteria for sepsis (life-threatening dysregulated host response to infection). The challenge is deciding when there is bacterial (or other) superinfection meriting an appropriate antimicrobial. There are now 15 references to COVID in the final draft, including to the SAPG's paper

Background		
Organisation	**Comments**	**Page and para / response**
Infection in Critical Care Quality Improvement Programme (PHE)	The inference that 'guidelines may become mandated targets susceptible to gaming' is not very helpful. Nearly all the colleges represented in the AoRMC produce guidelines and it does not seem the role of this paper to challenge that.	Page 6, para 2.3 We refer to gaming in this context because it exemplifies the potential for unforeseen consequences attendant on single interventions applied to complex systems. Best practice guidelines based on strong science positively affect clinician behaviour and patient outcomes, but when the evidence is weak, wrong, or accompanied by undesirable outcomes then challenge is a professional duty. Gaming was a common concern expressed during the first 10 years of the surviving sepsis campaign, and the debate continues today, not just for sepsis. See for example Sjoding MW et al. Gaming hospital-level pneumonia 30-day mortality and readmission measures by legitimate changes to diagnostic coding. Crit Care Med. 2015;43:989–95.
Northern Ireland Intensive Care Society	Explores and provides a balanced argument for the need for a nuanced approach. No changes recommended	Thank you
NHS England and Improvement AMR Programme, including collated comments from the Acute Deterioration Board	Very well written with good literature support. No other comments. Consistency required with the term antibiotics and antimicrobials in other places with consideration to giving definitions within the document.	Thank you
	Whilst the administration of antibiotics within one hour is not appropriate for many patients, and a more nuanced approach is needed, it is important the progress made on the rapid assessment and treatment of sepsis is not lost. The message must continue to be emphasised that the condition needs a rapid response, within the content of an approach which supports improved antimicrobial stewardship.	2.3 / 2.15; P6 & P8 We agree. And we also recommend that our proposals are subject to research evaluation.
NHS England and Improvement Professional & System	In community nursing it is important that the emphasis on rapid assessment and treatment of sepsis is reiterated within the context of taking action through escalation.	Indeed. This is the underlying theme of the report.

Leadership - Community Nursing	Good to have this highlighted later on in 17.2 on page 28	
UKCPA Critical Care Group	Clear and well presented.	Thank you.
UK Clinical Pharmacy Association (UKCPA) Infection Committee	Nosological is not a term I've ever come across, so may confuse some readers suggest "sepsis was inadequately recognised by health systems as a discrete diagnosis"	P5, 2.1 We use the term 'nosological' because it captures the general principle of classification, not just that of specific diagnosis. The diagnosis of sepsis must be placed within a terminological hierarchy.
	"non-specific secular changes over time" – I think the word secular here is unnecessary and has predominantly religious meanings	P6, 2.2 Removed. In the medical literature, secular change means changes occurring over time.
UK Sepsis Trust	*The term was first used (in the form 'antiseptic') in 1750 by Sir John Pringle who performed experiments testing acids and alkalis 'resisting putrefaction' [Pringle 1750]* We informally suggest Homer used the term a couple of thousand years prior ;)	2.1 We were referring to the word 'antisepsis', not the concept. You are correct in attributing the term 'sepsis' to ancient sources including Homer (σηψις = to rot) who described applying 'salves' to wounds, while the Edwin Smith Surgical Papyrus (circa 3600y ago) describes fever and pus in relation to wounds. However, the term 'antisepsis' was, to our knowledge, first used by Pringle.
	This guidance has been modified in the most recent iteration of the Surviving Sepsis Campaign's recommendations [Evans 2021] so that a three-hour window for administering antimicrobials for sepsis without shock is now permitted, recognising the very low quality evidence available. We would point out that this is not precisely what the revised guidelines state. They maintain a 1 hour recommendation for patients without shock in whom sepsis is 'definite or probable'	2.2 Thank you. We have added the word 'possible' to sepsis.
	In England, administration of broad-spectrum antimicrobials is part of a sepsis quality indicator [NHS England 2017] which mandates escalation to a senior doctor in the event of failure of patients with presumed sepsis to respond to treatment within one hour [NHS England 2019]. This is based on NICE guidance NG51 [NICE 2017] on antibiotic treatment for patients with suspected sepsis who meet high risk	2.4 Thank you for this caveat. We have revised this section extensively to clarify how this process evolved.

	criteria in the acute hospital setting, recommending that a broad spectrum IV antibiotic at maximum recommended dose should be given within one hour of meeting any one of the high-risk criteria. We are not certain that this was the case. We recall the first 2 years' iterations of the CQuIN incentive requiring screening in patients with an aggregate NEWS score of 5 or above, with treatment only in those patients (already therefore differentiated as sick) meeting one or more high risk criterion. We were not involved in the third year CQuIN, which was led (we believe) by Dr Inada-Kim.	
	The most recent iteration of the Surviving Sepsis Campaign's recommendations now accepts a three-hour window for administering antimicrobials for sepsis without shock, and recognises the very low quality evidence for such a recommendation [Evans 2021] See response to 2.2 above.	2.15 We have modified the text as follows: *The most recent iteration of the Surviving Sepsis Campaign's recommendations still requires broad spectrum antimicrobials to be administered within one hour of recognition for patients with possible septic shock or high likelihood of sepsis without shock, but now accepts a three-hour window for administering antimicrobials for possible sepsis without shock...*
United Kingdom Health Security Agency	Happy with this section.	
National Outreach Forum	Reference missing "……National Early Warning Score (NEWS-2) [REF] being…."	2.4; P6 Added here and at first mention in text.
	Incentivised rather than incentivized	2.11; P7 Done
Royal College of Nursing (RCN)	Suggest changing 'medical' to 'patient' review as the review may be undertaken by non-medical professionals i.e. Advanced Clinical Practitioners.	2.5 Done
Department of Health and Social Care	Useful references to published literature demonstrating the complexity of the issue and factors at play.	
	Could provide differentiation between 'sepsis' and 'septic shock'.	2.1 We will include a Taxonomy of sepsis in the Appendix.
	Really helpful background and history. Could a brief summary of approaches to	2.1-2.5 We agree that this would be interesting – but it will not be

	sepsis(and where they are similar or differ) in Europe and America be provided?	short, as we would have to describe the many differing healthcare systems and regulatory approaches. We and others over the past 20 years have encouraged a harmonised international approach to sepsis management in the USA, Europe and many other countries and regions. The key message is that there is growing international consensus that mandating a 1-hr target for antimicrobial administration is only necessary for the most severe forms of sepsis.
	Very clearly reflects the contextual and nuanced circumstances clinicians operate in when dealing with suspicion of sepsis.	2.5 Thank you.
	It would be helpful to have more explanation around the point made in this paragraph.	2.13 Have changed the word 'questionable' to 'is currently a matter of debate' – as addressed in this report.
	Are there other international views which could be captured here?	2.15 We believe that we have captured the current international views in the cited literature and through the Surviving Sepsis Campaign which includes input from all world regions and most major health systems.

Aims and methods		
Organisation	**Comments**	**Page and para / response**
Northern Ireland Intensive Care Society	The aim could be bulleted separately to identify this at a quick glance.	Already a separate paragraph
NHS England and Improvement AMR Programme, including collated comments from the Acute Deterioration Board	Appendix needs number adding	P8 Will correct all numbering once editing finished.
UKCPA Critical Care Group	Clear and well presented	Thank you.
United Kingdom Health Security Agency	Using ONS data is limited usefulness I would imagine given the heterogeneity of causes of death listed	6.4, P10 All data sources are problematic. We have provided a taxonomy which might encourage a consistent approach to diagnostic classification.
Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI)	Some may point out the possible risk of bias(es) because the guidance has not been developed using a recognised systematic guideline development process such as NICE or GRADE (or at least it is not evident from this report).	We accept this criticism, also mentioned by the ICCQIP. We have not produced a formal guideline, but a position statement which we recommend should be subjected to research evaluation. However, we have used systematic reviews where these are available. Where evidence is weak or inconclusive even systematic reviews fall back on clinical judgement, and this position statement represents the views of a wide range of professional organisations. NICE are willing to review the evidence base beginning this year.
Royal College of Nursing (RCN)	We welcome that multidisciplinary experts were involved in the development.	
Department of Health and Social Care	Could a line be added on timelines for the consultation, responding to comments and iterations of the position paper?	We have added to Methods: "*The guidance was then circulated to a wider stakeholder group of professional organisations and special interest groups for review. Responses were reviewed by the working group to create a final version of the guidance.*'

Current position: narrative review		
Organisation	**Comments**	**Page and para / response**
Intensive Care Society	Statement stops mid-sentence.	Pg 17, 12.11 Formatting issue with Word. Will ensure visibility in next iteration.
	Focus on effect on mortality. Is there any evidence on the time to antibiotics effect on morbidity?	The literature on this is scanty. We reference the paper by Whiles et al in para 14.4, showing that progression to septic shock is associated with delay in antimicrobial administration between 5-6 hrs following presentation.
Infection in Critical Care Quality Improvement Programme (PHE)	The inference from this paragraph is that because a lot of patients with sepsis are elderly, prompt resuscitation and management is inappropriate. This seems inappropriate. Clearly a number of patients present with sepsis as a terminal part of their illness and active treatment may not be appropriate, but in many, sepsis is the primary illness and age is not a factor that should on its own determine decision making. Irrespective of this, the concept that sepsis is rare in younger age groups is misleading. Figure 2 suggests that sepsis suspicion in persons under 60 (arbitrary definition of young) occurs in many patients. Although the mortality is much lower than in the elderly it is still finite and is still higher than many other conditions. Urgent treatment is not unnecessary in these patients and a more nuanced and complex description is needed for this paper.	P10, 6.4 The elderly are clearly more susceptible to infection and sepsis, and in many it is co-morbid disease and frailty which drive treatment limitation decisions. We do not argue for a lesser standard of care for the elderly, but we do argue against the overly simplistic description of sepsis as being a largely preventable cause of death in this population. For both elderly and younger populations we have emphasized the utility of response predicated by NEWS2 score
	The inference from this paragraph is that the increase in secondary care antibiotics is driven (mainly) by the CQUIN. This correlation may in some small part be related to the CQUIN but clearly increased ED attendances and other changes in case-mix may also be playing into this. In addition, it is quite possible that the increase in use is entirely appropriate.	P14; 10.4 We have modified the text as follows: *4. A driver for this increased use in in-patients **may have** been the Commissioning for Quality and Innovation (CQUIN) scheme. While other factors could contribute, they are unlikely to have driven a doubling in the use of iv broad-spectrum antibiotics.*
Northern Ireland Intensive Care Society	It appears to be a series of recommendations on what to do and not as part of the narrative review of evidence as statements such "should be" is used. This is followed by the antibiotic stewardship section. So the box 11.4 with the following	Box 11.4 We have positioned the two text boxes to follow the text on Initial Antibiotic Prescribing Practices.

	points may be better placed under the following section or best moved to the following recommendations part of the document. Point 11.9 in this box has a "table X" – check accuracy.	
	Formatting of brackets in this point and similarly in a few other places (just being pedantic).	14.2 Corrected, thanks.
	"Confirmation that initial suspicion of an infectious process was subsequently borne out is frequently lacking"...consider rewording to "There is lack of confirmation of initial suspicion of infection" or something similar.	14.3 Reworded to: '*Infection is not confirmed in as many as 40% of patients admitted with a preliminary diagnosis of an infectious process'*
	A section on imaging could be beneficial	We have considered this, but the subject is large, and the document already long, so we have chosen to limit our focus.
NHS England and Improvement AMR Programme, including collated comments from the Acute Deterioration Board	The paper notes that the misuse of the term sepsis persists and suggests that the needed clarification around terminology will be forthcoming. However, improved definition of it is core to the framework being implemented consistently and appropriately. It would therefore be very helpful for this to form part of the final version of the framework.	6.8, P11 We will provide a Taxonomy of sepsis – currently in progress, and will be added to the final report.
	Correct labelling in graph to clarify that this is detailing guidelines for adult patients and remove duplication of gent/gentamicin in the x-axis label.	11.3, P15 figure 3 Corrected, and now in Appendix.
	The last paragraph is incomplete in the Monotherapy or combination therapy: key points text box.	P17, 12.11 A problem with Word text boxes. Will be attended to in final version
	It is important that the process for obtaining timely blood cultures and the role they play in diagnosis is appropriately reflected. In an optimised blood culture pathway, most blood cultures will flag positive within 8 to 12 hours of collection. A key failure point in the blood culture process relates to underfilled bottles rather than the process itself. Collecting the right volumes and getting a timely blood culture result will improve outcomes There could be significant benefits from the Academy linking with the work being co-ordinated by the NHSEI Chief Scientific Officer's team to improve the blood culture pathway, with appropriate cross-references within the framework.	19.1, P22 We have mentioned variation in sampling volumes as a problem. We have now added: '*Adherence to best practice in sampling volumes and timing is important'*. We would be delighted to link up with the CSO's team, thank you.

	Whilst recognising that the position on consistent, reliable use of NEWS2 in community settings is still developing, it is important that there is clarity on clock starts in terms of when antibiotics should be considered. For example, patients who might have a high NEWS2 score when the ambulance picks them up often have a reduced score after receiving fluids or an antipyretic in transit to A&E, calling into question if the first measurement should be used.	P28, 29.8 We agree. The work you and others are undertaking to improve community care will eventually pay dividends. At present, we propose that for hospital practice, the clock will start with the first documented NEWS in the ED or hospital. In terms of the impact of therapeutic interventions, we currently recommend that if patients deteriorate, then the therapeutic actions should be upgraded to the next NEWS band. It would therefore be reasonable that if patients improve with therapy, their priority is adjusted accordingly.
	The escalation chart does not align with wider PEWS escalation approaches and it will be important for this to be addressed. It is also important to reflect that, whilst NEWS2 has a degree of use in pre-hospital settings, PEWS is not used due to a lack of evidence. (Dr. Damian Roland**,** Consultant in Paediatric Emergency Medicine at University Hospitals of Leicester NHS Trust is a key link for this.)	25.3, P25 We have made contact with Prof Simon Kenny, Prof Roland and the SPOT programme. The PEWS bands we propose are harmonised with the new guidance from the national PEWS programme board.
NHS England and Improvement Professional & System Leadership - Community Nursing	Good infromation and well presented throughout Is the uptake of NEWS2 in community settings known or documented?	
UKCPA Critical Care Group	Well explained.	Thank you
UK Clinical Pharmacy Association (UKCPA) Infection Committee	Dosing of antimicrobials should be optimised and follow local guidance. Some centers are will be utilising a prolonged β-lactam infusion strategy as the standard treatment for sepsis or septic shock despite its unknown efficacy however there is substantial data to show it significantly improves target plasma concentration attainment without increasing the adverse event or the occurrence of antibiotic-resistant bacteria.	11.4 Broad or narrow spectrum antibiotics? Key points, P15-16 Section 11. We have added a note to this effect.
	Need to complete sentence. Ends with ' 'In the setting of treating sepsis in hospital, given the low risk of cross-reactivity, most clinicians will substitute cephalosporins or'	Section 12.11 The box is complete in our version. Text boxes are often problematic in Word – we will

		ensure fidelity of conversion of the final version.
UK Sepsis Trust	*Template guidance was piloted by frontline staff at each iteration.* The authors make this claim more than once, yet appear neither to offer evidence in support nor a review of the findings. We feel that such evidence would add to the narrative.	4.2 Piloting was conducted during the pandemic at UHB and UCLH and was formative in nature. In the circumstances we had neither the resources nor the time to conduct a formal evaluation. In the report we recommend research evaluation of the guidance as a more appropriate approach.
	In the UK, claims have been made of 52,000 sepsis deaths per year with a high proportion of preventable deaths [UK Sepsis Trust] This link is to an historic (from, we believe, 2018) letter to a charity supporter. We would humbly suggest that it might have been easier, more current, and robust to link instead to our website which states 'up to 48,000 deaths'; makes no claim around the majority being preventable, and cites supportive peer-reviewed evidence. We find the use of this particular link unusual, and wonder whether it might have been chosen out of convenience to the narrative?	6.1 We have removed the reference to your advertising and briefing note on 'Representing the UK Sepsis Trust' if you no longer use this. It is worth noting that the persistence of non-peer reviewed sources of information of this sort is potentially problematic – for example, the Tweet delivered by the then SoS for Health in para 6.4 seems to assume that the mortality figures presumably provided by the UKST's briefing note refer to preventable deaths. We have used instead your York commissioned report – thank you for providing this.
	A revised method calculates 47 475 suspected sepsis admissions for England, approximately 17 admissions per 1000 adults per year, with a mortality of 7.2% [Inada-Kim 2017] We humbly point out that it does not. We quote from the link provided: In 2013–2014, 47 475 admissions were identified in the Oxford AHSN region using the 'suspicion of sepsis' coding set, yielding a population estimate of 17 SOS hospital admissions per 1000 adults in a given year. The overall in-hospital mortality rate for this group was 7.2%, which represents 3440 deaths The claim in this paper is therefore false and pertains only to Oxford. Even if the link	6.1 Thank you for pointing this out. We have corrected the text as follows: *In the UK, using 'suspicion of sepsis' [coding of all bacterial infective diagnoses] in the Oxford Region in 2013-14 identified 17 admissions per 1000 adults per year, with a mortality of 7.2%, giving an estimated mortality for England of 66,096 deaths [Inada-Kim 2017]; the true number of confirmed bacterial sepsis admissions will be lower than this*.

	weren't checked, the use of basic maths would show this to be false: an incidence of 17 SoS admissions per 1000 adults across England would yield much higher numbers than quoted. If 81% of a population of 56 M are adults [ONS 2021], then 17 cases per 1000 adults would yield 952,000 SoS cases and 68,544 deaths as a consequence. Whilst of course these would not necessarily all be due to sepsis, other than from hypoxia/ hypercarbia as a consequence of pneumonia we are unclear as to the mode of death in people in a high income country with other common infections (UTI, peritonitis, cellulitis etc.) if not from sepsis. That there are around 1M admissions with Suspicion of Sepsis in England each year is further borne out in Table 1 of the document.	
	During 2011-2015, on average each year there were 39,544 sepsis admissions to intensive care units in England and Wales, these representing the most severely ill hospitalised patients. We support and of course recognize as true this statement. However, it doesn't tally well with the claim of only 47,000 admissions with 'suspected sepsis'; nor with the claim that 'true' sepsis is uncommon, nor with the claim that the majority of sufferers are elderly and frail (a cohort surely less likely to be admitted to intensive care?).	6.1 We discuss in some detail the difficulty of determining accurately the incidence of 'sepsis'. By contrast there is good evidence that the majority of sepsis admissions are elderly and frail – we rehearse this in para 6.4 and explain the difference between dying with sepsis and dying from sepsis – an important distinction when considering preventability.
	There is a pressing need for a standardised taxonomy for sepsis to emphasize the requirement for both infection and new-onset organ dysfunction, as defined by Sepsis-3 [Singer 2016], now incorporated in ICD-11. Misleading descriptions of uncomplicated urinary tract infection as 'urosepsis' and meaningless terms such as 'septicaemia' need to be jettisoned. We wholeheartedly agree.	6.8 The taxonomy has now been included.
	RCOG green top guidelines published in 2012 [RCOG 2012] and reviewed in 2017 [RCOG 2017] and the Sepsis Trust UK Inpatient Maternal Sepsis tool [UK Sepsis Trust] are widely used by UK maternity units though the underpinning evidence base is weak. Based primarily on general adult practice,	8.3 The document we referenced was available on the UKST website and came up first in our searches. If this is no longer current, we suggest you archive it. Following

	these emphasise the administration of broad spectrum antimicrobials within one hour of recognition of 'severe sepsis' [Green Top Guideline] while the UK Sepsis Trust's criteria include 'red flag' sepsis combined with evidence of acute kidney injury (AKI) Again, we find the use of historic tools surprising and potentially misleading. We humbly suggest that it would have been easier and quicker to find our current tool, which has been on our website since 2019. This commences, as per proposed AoMRC guidance, with a patient who looks unwell or has triggered (according to local protocol) on a MEOWS score. Tool available here	discussions with you we have now clarified that your up to date versions are contained within the UKST toolkit and have referenced this accordingly [UK Sepsis Trust 2019]. We have now also received a response from the RCOG and have therefore referenced their work in progress on maternal sepsis.
	A 7.5% reduction in total antibiotic use (as defined daily doses [DDD] per inhabitant in England) has occurred recorded over a 5-year period from 2015-19. However, this relates to decreased use in primary care (-12%); during the same period hospital in-patient use has increased by 13% and outpatient use by 1.7%. Again, we humbly suggest that this is not precisely what was reported, or perhaps was interpreted to suit a purpose. Copying directly from the linked ESPAUR report: From 2016 to 2019 the rate of antibiotic use in secondary care increased by 1.9% (4,586 to 4,674 DDDs per 1,000 admissions). Between 2019 and 2020 there was a 4.8% increase in total prescribing rate (4,674 to 4,899 DDDs per 1,000 admissions). This increase was driven by a rise in the rate of inpatient hospital prescribing (using the metric DDDs per 1,000 admissions), thought to be largely related to reductions seen in hospital admissions (the denominator) and changes in hospital populations since the start of the pandemic.	10.2 We used the data in the ESPAUR 2019-2020 report. The ESPAUR 2020-2021 report was published after we circulated our draft. We have now included a reference to the new report and show the antimicrobial prescribing rates from 2016-2021 in the Appendix. However, as the 2020-2021 report includes the start of the Covid pandemic, the data are unlikely to be representative of the previous 5 year trend.
	Lactate measurement should therefore be regarded as a valuable 'single parameter' adjunct to vital signs measurement. Again, we fully agree.	23.2
United Kingdom Health Security Agency	Would say amoxicillin-clavulanate rather than coamoxiclav	11.3, P15 Done.
	Numbering gone awry in text box	12.5, P17 Numbering is provisional in this draft.

West Midlands Adult Critical Care Network	It would be better to have figure 1 next to the paragraph that first mentions it – ie para 6.2	6.2 and 6.5 Moved.
	Again move fig 2 next to the para that first mentions it	6. 4 and 6.6 Moved
	'The disease burden is mainly in children under 5 years old, largely due to vaccine-preventable meningococcal and pneumococcal infections. The causative organism remains unidentified in approximately half.' '...largely due to...' implies the majority have an identified organism causing the sepsis, which contradicts the following sentence.	7.3, 12. We have clarified this as follows: In Europe, mortality in children admitted to hospital with sepsis is low. The causative organism remains unidentified in approximately half. Mortality in community-acquired infections was associated with identification of the causative organism, presence of sepsis, increased PICU admission, oxygen or respiratory support requirement (or both), inotrope administration, and prolonged hospital stay [Martinon-Torres 2018]
	Table X – currently missing... but may turn out to be 32.1 appendix table 1?!	11.9, 16 Thank you. Corrected.
	The box, 12.5, cuts paragraph 12.4 in half	12.4 & 12.5, P17 The formatting will be fixed in the next iteration.
	'...low risk of cross-reactivity, most clinicians will substitute cephalosporins or'? the rest of the sentence appears to be missing	
Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI	Agree that for surveillance purposes updated case definitions are required. Should the narrative clarify what categories should be included to capture the most relevant information? E.g. patients with proven infection and clinical features consistent with sepsis, and then, patients with no positive cultures, but clinical features consistent with sepsis and no alternative diagnosis, etc. It could get quite complicated.	6.8 We agree that this is an important issue, but as the report is already rather long we feel we should resist the temptation to explore definitions in detail, because our primary focus is on proposing that the route to identifying sick septic patients is through a generic measure of severity of illness.
	Very good to see discussion of the 48h antibiotic review. Would also like to see some comment on this in the Synthesis and Recommendations. Appreciate that the paper is focussed on early clinical decision support, but some comment on what happens over the next 24-48h If the patient improves would be good. De-escalation might be appropriate.	12.2 We have added a statement recommending limited duration (5 days) if the patient's condition is improving.
National Outreach Forum	Necrotising rather than necrotizing	14.6, P20; and 16.1, P21 Done.

	Randomised rather than randomized	15.1, P20 Done.
Royal College of Nursing (RCN)	The current position also puts unnecessary burden to already deprived nursing and medical workforce to perform tasks such as obtaining IV access and IV antimicrobials within an hour when there is no benefit for patients who are Septic not in 'shock' state.	5.1 Agreed. We mention the impact on workload in para 2.4.
	We welcome the clarity on current data around incidence of sepsis and to understand that the real incidence is much lower than previously reported.	6.1 Probably....but the fact is we don't actually know, because sepsis is such a pleomorphic entity. There was an error in our first draft (see discussion above) which has now been corrected.
	Shankar-Hari (2016) highlighted declining mortality over the years. This could be due to better awareness, recognition, education, early warning scores and Critical care outreach teams.	6.1 Yes, all these mechanisms are possible. We reference his paper in para 6.2.
	What is the plan regarding incorporating UK National maternal early warning score (MEWS)?	8.3, P13 Please note responses to RCOG.
	Should it be explained why there is variance on antimicrobial prescribing guidelines for treatment of sepsis of unknown origin?	11.2, P15 These variations are multifactorial in origin – sometimes related to local purchasing agreements, or microbiology and infection control familiarity, or local resistance patterns. This topic lies slightly outside our remit, and so we chose to draw attention to this variation rather than explore the reasons for it – which are the remit of groups like ARHAI.
	This is such an important information. Can this be provided in a table format please?	13.2 The data are available in the ESPAUR reports. As detailed information on resistance is not the main focus of our paper we have had to limit the decription to this brief paragraph.
	We welcome the clarity you provide here. Many healthcare professionals and organisations are penalised for poor outcome without taking into consideration on age, co-morbidities and frailty.	17.1 Thank you. We do agree.
	Blood culture: there is big emphasis on obtaining blood cultures particularly prior to administration of IV antimicrobials in clinical practice. The reasons why blood	19.1, P22

	cultures are not taken may be due to availability of skills to perform venepuncture and logistics (availability of blood culture bottles – major barriers in clinical practice). Can we also emphasise the importance of wound swabs, sputum, and urine samples here?	We have added a sentence to the start of this paragraph.
Department of Health and Social Care	It would be helpful to have statistics for likely deaths in sepsis in the UK broken down into age groups if possible.	6.1 Does the Fig on 'suspicion of sepsis' not provide this information?
	Helpful summary. Should the extent of 'just in case' antimicrobial prescribing be acknowledged here?	6.2 We mention the impact of uncertainty on prescribing practices in paras 5.1 and 19.1
	Is Europe assumed to include the UK?	7.3. In this context, yes.
	CQUIN??	What is your question please?
Royal College of Paediatrics and Child Health	The section on paediatric sepsis has limited relevance to neonatal sepsis. A distinction between neonatal and paediatric sepsis is relevant given recent work around NICE vs Kaiser Permanente Sepsis Risk Calculator use in neonates [NICE NG195 guideline review; and NEWTT2 currently being tested in the identification of the unwell neonate. Pre/intrapartum events are a factor in the antibiotic use in neonates, and this is also not mentioned in the obstetrics section.	This guideline does not include neonates, as that would be a completely different document in itself. The NICE sepsis guidelines [NG51] also excluded neonates, as there is a separate neonatal sepsis guideline [NG195].
	There are overarching principles that can be applied irrespective of age i.e. the use of narrow-spectrum antibiotics in situations that are not time-critical or after 48-72 hours, and the use of shorter courses of antibiotics, however a clearer distinction between adult and paediatric sepsis is required.	This is recognised in the separate adult and paediatric sections. There are significant differences in the approach to sepsis management between adults and children. The Sepsis-3 criteria were derived from adult patient databases. There is a paediatric version [Matics et al 2017] and we have referenced this in the text. Paediatric practice in the UK encompasses a wide age range from neonates through to young adults, which are characterised by variations in physiology, immune responses and specific responses to infection. The ability to physiologically compensate for serious illness is limited in children, providing a shorter window of opportunity for clinicians to recognise the signs and to respond quickly, to avoid

		the progression of deterioration to become critical. There is age - appropriate variation in physiological signs including heart rate, respiratory rate and blood pressure, from birth to adulthood
	It should be recognised that although mortality is significantly lower than adult populations, there is a difference in the presentation, risk of deterioration and admission rates within the paediatric population of varying age groups (the 'Suspicion of Sepsis' graph clearly shows a majority of the septic episodes is in the 0-4 years age group).	Agree, see above. We do not use mortality as an outcome measure, as (fortuinately) it is a relatively rare outcome; admission to critical care is a better surrogate measure.
Royal College of Obstetricians and Gynaecologists (RCOG)	There's no separation of care for very young babies – children under 16 are clumped together as one. My understanding is that care for very young babies should be different from that in older children, especially before age 3 months, and not least because of group B Strep sepsis, and therefore there should be a separate section or recommendations relating to these patients, drawing on research relating to them rather than extrapolated from older populations. There's no mention of NICE's Neonatal Infection guideline, which was published in April of this year and I'm sure has relevance	Neonatal sepsis is indeed a most important topic, but not one which we feel we can include here. It deserves a separate review. We have now mentioned neonates under 'limitations' towards the end of the report and provided a reference to the NICE guidance. Inclusion of neonates would necessitate a whole new section, as neonates can be managed in Neonatal Units/ICUs (inborn) or after discharge from hospital when they present to a children's hospital/ED/Unit. The management and approach is very different, and neonates are not usually included in sepsis guidelines for children.
	I've reviewed the document and have no particular comments. It was a very interesting read, and suggests a necessary change in assessment of sepsis in its Clinical Decision Support Framework.	Thank you.
	I am concerned that the MEWS chart is not referred to. If Sepsis management is to be merely closely linked to the NEWS, this may be detrimental to the obstetric population. I note there was no RCOG rep or obstetric physician amongst the participants.	See above. A MEWS-specific chart can be produced subsequently. As the RCOG did not respond to initial invitations to join the working group, obstetric input was provided through obstetric anaesthesia and critical care. RCOG guidance has now been provided through the stakeholder consultation.

	They mention there were lay representatives, but there's no mention of them in the Participants' List.	Mr Peter Gibbs, head of ICUSTeps provided our PPI input and we are grateful to him and them for this. The full list of working grioup members is now included.
	We said in our statement in response to the media reports of the two maternal deaths from HSV-1 (herpes simplex virus) this week: *Routine investigation and management of postpartum maternal sepsis should always consider viral sources of infection and appropriate changes should be instituted to support earlier diagnosis and appropriate treatment.* I couldn't see anything in this document about considering a viral source of infection.	Thank you for identifying this omission. We have added a sentence and references on herpes infection to the end of para 8.1.
	Much of the guideline isn't really relevant to the pregnant population given the reliance on vital sign scoring approaches or other assessment modalities that would not be appropriate to use in a pregnant population.	We may not have understood this comment. We appreciate that pregnant physiology differs from the non-pregnant state, which is why the Maternal Early Obstatric Warning Score is employed instead of NEWS. The new RCOG sepsis guidance uses 'red flag' criteria, which derive from the UKST's guidance which includes MEOWS.
	There are multiple reasons for maternal susceptibility for infections in pregnancy, but the change in peripheral T cell profile is controversial and there is no good evidence that this factor makes a major contribution to the problem. The review referenced here does not discuss the issue of how maternal immune adaptation to pregnancy predisposes to infection and is focussed on pregnancy loss and pre-eclampsia. I would suggest a broader statement that encompasses the physical changes (reduced lung residual capacity, urinary stasis, immunological changes, pregnancy specific risk factors such as gestational diabetes and preterm prelabour rupture of membranes, alongside the increased exposure to surgical procedures such as caesarean section would be more accurate in capturing the range of contributory factors. [Kourtis et al 2017]	Para 8.1 Thank you for this suggestion. The paragraph has been modified to include the following: "*Factors which may enhance susceptibility to certain infections include altered physiology such as urinary stasis or a reduction in lung volumes, the development of gestational diabetes or pre-term pre-labour rupture of membranes, the increased exposure to surgical procedures such as caesarean section, and changes in cell-based immunity [Kourtis 2014]".*
	"In the absence of AKI, the UK Sepsis Trust guidance extended the window for antimicrobials to three hours [UK Sepsis Trust 2019]." This statement is not consistent with the guidance in the source	Para 8.3 Thank you for pointing this out. As mentioned above (UKST), we have checked this with the UIK Sepsis Trust. The flowchart on their

	cited (the UK Sepsis trust manual) or with their currently available tools on their website. In which the 1 hour time threshold is very clearly communicated.	website was a legacy document from 2017 which has now been superceded by their 2019 toolkit. We have revised this section of the paragraph as follows: *"The Royal College of Obstetricians and Gynaecologists' [RCOG] 'Green Top Guidelines' published in 2012 [RCOG 2012] and reviewed in 2017 [RCOG 2017] and the Sepsis Trust UK Inpatient Maternal Sepsis tool [[UK Sepsis Trust 2019] are widely used by UK maternity units, though the underpinning evidence base is weak. Based primarily on general adult practice, these emphasise the administration of broad spectrum antimicrobials within one hour of recognition of 'severe sepsis' [Green Top Guideline] while the UK Sepsis Trust's criteria include 'red flag' sepsis combined with evidence of acute kidney injury [AKI]. The RCOG is currently revising its sepsis guidance."*
	The RCOG are due to be releasing the sepsis following pregnancy guidance shortly which can be added as a link when complete.	RCOG Guidance on Identification and management of maternal sepsis during and following pregnancy: awaiting publication

Synthesis and Recommendations		
Organisation	**Comments**	**Page and para / response**
Defence Medical Services	The review of the evidence of the management of serious infections and the continued rationalisation for antimicrobial stewardship is very much welcomed.	Thank you
Royal College of Physicians	Within the main body of the report, you state *If the attending clinician has particular concerns about the patient's condition or if additional information from laboratory tests indicates specific conditions of concern such as additional organ dysfunction or neutropenia, the severity status and accompanying actions should be upgraded according to patient need,* ***and at least to the next NEWS band.*** This wording is appropriate. However, in the executive summary you state *the clinician can 'upgrade' the actions required* ***to those of the next severity band.*** We support a more flexible upgrade as described in the main report of ***and at least to the next NEWS band,*** this should be stated in the executive summary in those words. This must also be replicated in the figure. The use of the highest NEWS2 during the presenting episode to guide timing of response should also be clear on the figure and in the executive summary. In the notes to accompany Figure 1 it states *NEWS-2 should be used in conjunction with clinical assessment, not to replace clinical judgement.* This statement is consistent with the RCP position on NEWS2, and is consistent with our recommended edits above. We recommend that the wording in these notes is also changed to ***upgrade actions by at least one band***	Executive summary and the Figure and accompanying guidance notes have all been changed to state ***at least to the next NEWS band***.
	There is some inconsistency between the notes accompanying the figures for adults and paediatrics. It would be helpful if the wording was more consistent. The Paediatric guidance notes contain a statement on parental concern, and this could be replicated in the adult notes by patient, family or carer concern. The paediatric notes also contain a statement on other urgent management which is absent from the adult notes, we recommend that this is replicated in the adult notes. If these changes can be made, then RCP can endorse the recommendations.	We have harmonised the wording of the row labels. We have added 'or carer' to the adult guidance as follows: "*If clinical or carer concern about a serious diagnosis, continuing deterioration, neutropaenia, or blood gas / lab evidence of organ dysfunction, including elevated serum lactate, upgrade actions at least to next NEWS-2 level →* " Thank you.

	2.2.1 *a significant proportion of patients cannot benefit* is changed to *a significant proportion of patients do not benefit.* As you do not site direct evidence of early broad spectrum antibiotics causing antimicrobial resistance *contributing to increased antimicrobial resistance* should be prefaced by *likely to be*, 2.6.2 *must be completed within 6, 3, or 1 hour* may be more appropriately worded as *should be completed* 6.1.1 the statement *Clinicians must therefore act under uncertainty, but are judged with hindsight, and usually on the basis of process audit rather than patient outcomes.* Requires qualification, as no evidence for this is provided. We do not believe it materially adds to the document, so removing or rewording this statement could be considered.	All modified accordingly. We have retained the statement about being judged with hindsight as anecdotal evidence suggests that junior clinical staff prefer to administer antimicrobials when there is doubt about sepsis rather than have to justify their omission on subsequent case review.
Intensive Care Society	I like the tables but am a little unsure why the adult one indicates probability of infection while the paeds one mentions sepsis. I think that both are possibly a little complicated and I worry that giving antibiotics/doing certain things might slip through the net. This is much more complicated than 'if you think the patient has severe infection give antibiotics within 1 hour'. I do wonder whether there should be more focus on antibiotic stewardship and choice of antibiotic rather than whether to give in the first hour etc.	Harmonised, thank you. The decision support frameworks are as synoptic as we could manage. If we add more info, they will only become more complex, as we show in section 9/10.
ICUsteps	Does NICE review other organisation's guidance as part of their review process for guidelines? My understanding was that they review new RCT evidence/systematic reviews and other high quality evidence, but are unlikely to review other organisations guidance.	30.1 We have had a very positive meeting with NICE and it is possible that they will convene a review group to review the evidence based on our report.
Infection in Critical Care Quality Improvement Programme (PHE)	The statement 'Now, some twenty years later, with new research findings available, we propose a modest 'course correction' which makes space for clinical judgement in the urgency and timing of administration of antimicrobials, within an accountable clinical decision framework based on severity of illness as proposed by the National Confidential Enquiry into Patient Outcomes and Death and NHS England.' Given that this is exactly what the international guidelines published earlier	P27, 28.1 There is indeed a growing international consensus that the 1-hr mandate can be relaxed for patients with less severe forms of sepsis where there is uncertainty about the diagnosis. Our course correction is to anchor treatment priority in NEWS-2, so this is a relatively novel recommendation which adds to the international position. The Academy working group does not consider this

	this year have done, this course correction may now be superfluous.	superfluous, but a useful addition to the excellent work done by the SSC and other groups
	Decision support tool. I do not follow the logic as to why the NEWS score has been used for this tool. The authors involved in this paper have described and published the qSOFA score as being the best marker of severity for patients with sepsis. As it is simpler to use and quantify and if it is a better marker of severity in this condition, then it would be intuitive to use in the tool.	P27 There are variable conclusions from papers comparing scoring systems for sepsis, as described in the report. We have chosen to recommend NEWS-2 because it is now nationally adopted as the generic indicator of severity and monitor of deterioration. It seems pragmatic and sensible not to promote a parallel system. By placing it at the start of the decision tree, we replicate clinical throught processes – 'Is this patient sick?' – which can then be followed by 'Is this patient infected or septic?'. The use of NEWS provides an objective method for stratifying clinical priorities and triage in a manner which lends itself to research evaluation. The Sepsis-3 analysis did not promote qSOFA as the 'best' marker of severity but simply highlighted this would very quickly detect patients at high likelihood of having sepsis. As NEWS-2 already incorporates qSOFA criteria and 4 more, and is used nationally, it is best to stick to one universal system. Incidentally, the recent SSC guidelines did not recommend use of qSOFA but failed to offer a preferred alternative.
	The statement 'For the avoidance of doubt, it should be emphasised that these time frames are indicative, not mandatory' seems out of place. This assessment of how significant (or strong) a recommendation is, is usually performed by providing a gradation of the recommendation itself. The paper seems to be falling between two stools recommending a course of action and then saying that it does not need to be followed.	P28, 29.7 We have revised the text to clarify that if actions can be completed earlier that the maximum then they should be. We note that the SSC guidelines now incorporate the word 'ideally' in terms of meeting time targets, and it is not clear to us what this means in terms of meeting a standard. We have therefore avoided offering the opportunity to take longer over a task, but providing more time in the first place for actions to be completed.
	International guidelines and sepsis bundles now describe the time zero as the time of recognition of the sepsis rather than the	P28, 29.8 NEWS is a hard metric for all-cause deterioration – while recognition of sepsis is clinician-dependent and

	time of triage (which is when the NEWS-2 score will probably be first completed).	follows (not precedes) the initial assessment of severity. A high NEWS score should prompt a prompt and appropriate response whatever the cause, so our hope is that these very sick, high-risk patients would be prioritised over lower acuity patients.
	Decision Support Tool. Recent guidelines now in support of a three-hour delay to giving antibiotics in those patients with an infection where sepsis (without shock) is possible to allow for a diagnostic work up from the time sepsis is first recognized. It is acknowledged that this three-hour threshold is arbitrary, although has now received widespread international consensus. I am unclear why in this paper six hours has been chosen. This seems as arbitrary and as it is against the international view may add confusion to practice with little evidence base for change.	P29 We have used NEWS-2 to define priorities because, as presented in the report, there is now a reasonable body of evidence that the infection point for mortality rates is at a NEWS of 4-5 points. This is comparatively simple for clinical staff to interpret and action, and is accompanied by harder evidence than using single indicator measures such as 'red flag' sepsis or the NICE 'high risk' indicators. Six hours was our maximum time limit for the reasons we provide in paras 14.1 and 14.2. The increase in mortality associated with time to antimicrobials in all-cause sepsis starts around 5-6 hours. We have emphasized that treatment should begin within 6 hours and there should not be any administrative delay once infection is deemed treatable
	Decision support tool. Sepsis as defined is a life-threatening systemic response to an infection with organ dysfunction. There will therefore be very few patients who present with sepsis and have a NEWS score of zero. This may confuse readers into misunderstanding what sepsis is.	P29 Our clinical decision support framework is applicable to patients without sepsis as well as those with sepsis. As stated above and in the report, the approach we have taken is to consider clinical practice from the perspective of the bedside clinician – 'is this patient sick?' precedes the question'is this patient septic?' We ask clinicians to consider the likelihood of <u>infection</u> – not sepsis. It is entirely possible for infection and zero NEWS to coexist. Infection becomes sepsis once there is evidence of new organ dysfunction.
Scottish Anti-microbial prescribing Group	"In SAPG there is significant concern and focus of review of the antimicrobial/infection management plan to minimise unnecessary antibiotics. We are therefore keen to promote early IVOST and	Thank you for the link to your excellent programme. We have altered the intervals for AB review to 48-72 hrs for NEWS 5-6, and NEWS ≥7.

[SAPG] via Deputy NCD	shorter duration therapy whenever possible particularly when there has been time for a clinical response and for culture results are available. As such a specific 72 hour review might be captured within an additional line at the bottom of table – this would also dove tail with our SAPG Hospital Antibiotic Review Programme.	
	Additional concerns and comorbid disease – think these are useful additions. Generic actions – agree	
	Clinical likelihood of infection "Possible": divisions between NEWS-2 0 and 1-4 are artificial so should be merged: "within 6 hours: microbiology tests, source identification and control plan. Consider antimicrobials [administer, revise or defer] based on clinical scenario" Clinical likelihood of infection "Probable or definite": suggest remove the NEWS 0 box and merge with NEWS-2 1-4 – no change to the text in NEWS-2 1-4	The reason we have retained a NEWS = 0 band is that we want to emphasise the continuum of severities and highlight the difference between infection and sepsis.
	D/w Infection specialist if uncertain could be pasted in all the boxes for Possible or probable/definite irrespective of NEWS. However should also mention following guidelines regarding required investigations.	We did not want to impose an undue workload on ID/micro for the large number of low-risk patients. Where sepsis occurs [higher NEWS] the working group wanted to ensure that ID/micro were well-integrated in the clinical pathway. Hence the difference.
	NEWS 5-6: Within 48 hrs - Review antimicrobials – suggest remove reference to ID/Micro as empirical guidelines provide advice and IV to oral switch options. If any blood cultures are positive, ID/Micro will contact the team. If the patient is not improving with empirical treatment after 48-72 hours then appropriate to contact an infection specialist.	There may be considerable variation between different parts of the UK and between Trusts in how closely ID and Micro are involved. We would prefer to retain this emphasis on the need for close collaboration.
	NEWS >=7: with 24 hours – Review antimicrobials – suggest reference to micro/ID as above. Also suggest that reviewing within 24 hours is too soon and should be 48 hours as per 5-6	We have modified this to 48-72 hrs.
	The review aspect of the guidance could be expanded. Suggest that 48 hours is often too early to be definitive with an infection management plan. The bottom line of the table could be devoted to a 72 hour review for those with possible or probable/definitive infection– irrespective	We appreciate the need for fine-tuning this aspect of antimicrobial stewardship. However, the framework needs to be as simple as possible and to focus on the initial management of the septic patient. We hope that by specifiying the need for collaborative review, this will

	of initial NEWS-2 score. Suggest something like: — 72 hours Review and document infection management plan — Review clinical response, laboratory and radiology results and consider source control — Consider IVOST/ Stop/ De-escalate / Infection specialist review — Record plan and limit duration of antimicrobial therapy per local guidance	capture the important points you make here.
	Role of infection specialists – they should be more accessible in acute medical and surgical areas and able to provide consultation on all acute inpatient areas but appreciate difficult to describe within this matrix. Medical receiving units should have routine input from infection specialists to not only identify those who should go to a specific ID bed but also for stewardship issues.	We do agree about ready accessibility however this is beyond our remit. In intensive care there are close collaborative relationships between the intensive care specialists & microbiology, and it would be wonderful if this could be levelled up across the whole hospital.
Northern Ireland Intensive Care Society	This is a easy to use framework supported by good supportive evidence at the level of the "unwell" patient but when it reaches the clinical likelihood of infection, it introduces 3 possibilities of unlikely, possible and probable which are not currently defined. This introduces uncertainty where there may be an increase in antibiotic use especially in the NEWS 1 – 4 cohort. This could be left as pragmatic local decision but would lead to differences in classification between clinicians and sites.	P29, Figure 4 Clinicians will use objective measures of likelihood of infection where these are available in the initial stages of presentation, but they still have to take a clinical judgement. If there were an objective measure or set of measures available we would incorporate them – we discuss these difficulties extensively in the report.
Royal College of Emergency Medicine [RCEM]	National PEWS - Throughout these sections, the terms 'PEWS' and 'national PEWS' are used interchangeably. However, the suggested PEWS score [SPOT] is not given, and is also not available in the references/hyperlinks. As this is more controversial than NEWS2, and less universal We would suggest: 1: making this scoring system easily available in reference/hyperlink 2: Acknowledging further that no nationally agreed score exists, and explain the rationale for choosing this PEWS above others.	p26, p29 This has been changed and PEWS bands amended to align in the Table. We will adjust so that this is the hyperlink from the PEWS programme board
	Time zero is defined as first NEWS score in ED. Whilst this seems sensible, currently there are well publicised delays to handover from ambulance, and delays to initial assessment. This is an opportunity for	29.8, P28 We have added arrival 'at hospital' to para 29.9. We have added the following guidance to the frameworks: *Time*

	gaming. There are also issues regarding service design and 'initial assessment' vs streaming/triage etc which are of concern with time based metrics We would suggest: 1: a statement that delays to initial assessment in ED, with observations to enable NEWS to be calculated should be avoided, if 'time zero' is first observations.	*zero = first NEWS-2 on presentation to ED, but clinicians should take into account lag-time bias (NEWS-2 recorded in the community, or in the ambulance) and changes in the patient's condition which might indicate the need to upgrade actions and timelines*.
NHS England and Improvement AMR Programme, including collated comments from the Acute Deterioration Board	Although the proposals emphasise the importance of clinical judgement, it is important this is further underlined. There is a risk that by starting assessments with the NEWS2 score it implies that decision making is driven primarily on scores and not on clinical acumen.	28.1 , 29.7 , 2.14 P27 / 28 / 8 NEWS-2 is a generic measure of severity of illness and deterioration. We support existing national guidance in using it in this way. The frameworks provide an accountable method for allowing clinicians to exercise their judgment in providing initial supportive treatment while making a timely diagnosis.
	Suggest adding pharmacy staff and healthcare assistants to the list of staff needing to engage in the adoption of frameworks at local level.	30.2, P29 para 3 We have added 'and allied health professionals' to this para.
	Consider the practicalities of creating the expectation that ID or micro should review all patients with NEWS2 scores of 7 or more within 24 hours (and 5-6 within 48 hours). Staffing and workloads are unlikely to be sufficient to allow this at all hospitals, especially on weekends and bank holidays and I have not seen evidence to support this recommendation. Suggest amending to senior clinical review and align with start smart then focus guidelines (e.g. ST3 and above, ID/micro review or AMS specialist pharmacist).	30.4, P29 Figure 4 We have added 'senior clinician' to the guidance to review with ID/Micro.
	Suggest adding need for review of antimicrobials at 48-72 hours to the column for NEWS2 1-4.	We have added 'and review' to 'D/w ID/micro if uncertain'.
	Is there clear evidence to suggest that delaying antibiotics to within 3 hours for neutropenic patients with a NEWS2 score of 4 (as per suggestion to move one severity column up) is safe and appropriate? And have haemato-oncology specialists been consulted on this? I can't see representation from this clinical group on the participant list so would suggest that further consultation is sought, and	We have discussed our guidance with the British Society of Haematology. They accept that current practice is not well-evidenced (ie: antimicrobials for febrile neutropenia) but is so well established clinically that it will be difficult even to research. We have added text to that effect, while noting that the current literature

	consideration given to whether NICE 151 should be reviewed.	does not support rushing in with antibiotics [Koening 2019].
	It is unclear whether this table and explanatory text relates to antibiotics or antimicrobials. The term "broad-spectrum antimicrobial" is likely to be interpreted as antibacterial therapy. Clarity is needed on whether this guidance relates to antibacterials, antifungals and/or antivirals (or other treatments for viral infections). Viral infections such as flu and COVID-19 may cause high NEWS2 scores, but use of broad-spectrum antibiotic is not always necessary.	We have simplified all terms to 'antimicrobial'. We have added the following text to the Methods and to the guidance accompanying the frameworks: *The term 'antimicrobial' is used throughout to cover antibacterial, antifungal and antiviral agents, but in the guidance on the time intervals available for initiating treatment we refer specifically to antibacterial agents. Identifying non-bacterial pathogens may take longer than the time intervals specified.*
	We would suggest the guideline emphasises that lower risk patients should be treated according to local guidelines for the likely source of infection rather than with broad-spectrum antibiotics as standard.	We have added the following statement to the guidance attaching to the frameworks: *Reserve broad-spectrum antimicrobials for higher risk patients when the infective agent has yet to be characterised.*
	i) Review inclusion of treatment within the assessment section (or explain rationale in text) ii) Why is there no probable infection category in paediatric patients? iii) Consider adding explanation of why the table formats are different in adults and paediatric recommendations. iv) The abbreviations used within the table should be defined.	30.14, P31 Figure 5 i) We have changed the label to 'initial generic actions'. ii) & iii) In children presenting to the ED with possible sepsis, there are a number of clinical presentations where possible, probable are indistinguishable from definite sepsis. Examples are: bronchiolitis vs bacterial pneumonia, enterovirus sepsis in an infant < 6 months with shock vs septic shock secondary to bacteraemia (E.Coli, S Aureus, GAS), viral gastroenteritis with shock vs septic shock secondary to bacteraemia (E.Coli, S Aureus, GAS), prolonged febrile convulsion vs meningitis. iv) We will provide a list of abbreviations as well as a Taxonomy.
	Appendices numbering is not consistent.	32 Will be fixed in final edit, thanks.

	If they are not already engaged in doing so, it would be very helpful for HEE to produce a learning module rather than just relying upon local initiatives for awareness and application of the framework.	n/a Thank you for the suggestion. We will follow this up once we have obtained approval or endorsement from all bodies.
NHS England and Improvement Professional & System Leadership - Community Nursing	22.2 Would be useful to highlight that community settings need immediate access to risk scoring tools and also to highlight the benefit of shared clinical records 25.2 would be good to menation 'community' here as community is a major part of all care pathways	We agree, and this is an area of active search. We cannot make strong recommendations though, as this is a matter for the NHS(E) Acute Deeterioration Board. Please also note our response to the RCGP.
UKCPA Critical Care Group	"Appropriate" treatment is recommended. This should include ensuring that the dose is also appropriate. In many cases currently the initial dose may be reduced inappropriately due to perceived organ dysfunction, or the patient weight is not taken into consideration. Under-dosing may affect success of treatment and lead to resistance.	Sect 15 Agree – and also other guidance such as intravenous infusion rather than bolus dosing. But outside our remit in this case.
UK Clinical Pharmacy Association (UKCPA) Infection Committee	Do you want to explicitly give each band a name similar to "red flag sepsis"? This could be an opportunity to explicitly call out that the initial stage of diagnosis is only a "suspected sepsis". A patient could be identified as having "yellow/amber suspected sepsis", "amber/gold/brown suspected sepsis" or "red suspected sepsis" within the ED and then on the acute admissions unit, there would be more clarity on the steps for the receiving clinicians?	P29 We understand the attraction of colour-coding. The problem is that these 'red flag' and 'amber flag' criteria have limited validity in terms of predictive utility. Moreover, if we use them, there will be confusion with the pre-existing systems.
UK Sepsis Trust	*For adult patients (Fig 4) the working group members were unanimous in making an assessment of illness severity the point of entry, based on the NEWS-2 score, in four bands: 0; 1-4; 5-6; and ≥7.* We don't see a clear inflection point at NEWS = 7 in Matt's work, but fully understand the need for pragmatism. Could this be explained more fully? https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7330211/	29.2 [Smith 2013] and RCP guidance Fig 2: progressive increase in mortality risk from around NEWS=4, and clearly higher risk with NEWS 7 and upwards. We chose 7 as this seems to be an inflection point between 6 and 8, with a composite adverse outcome rate of around 6%. The RCP defines clinical response thresholds as 5-6 being an urgent response threshold, and 7 or more as the emergency response threshold. Using these thresholds, Inada-Kim 2020 showed marked increases in mortality risk at 5 and 30 days post-admission. A systematic review of studies of non-ICU patients [Zhang 2021] found that a NEWS of 5 provided the most

		sensitive single cut-point for mortality, while an ED study [Masson 2020] found that NEWS-2 of 4 or more was the best single cut-point. We have therefore selected 1-4, 5-6, and ≥7 as clinically relevant step changes in risk consistent with current guidance.
West Midlands Adult Critical Care Network	'…within 4 hours (PEWS 1-4), within 3 hours (PEWS 5-6), or within one hour (NEWS ≥7).' I think the final NEWS should be PEWS. Also check the numbering – for children the ranges would appear to be 0, 1-4, 5-8, >9, above figures seem to be the adult figures	29.4, P27 Thank you, and apologies for these errors, now corrected.
	While it may extend the guidance, it may be clearer if the adult and paediatric information is separated out. Alternatively, move the figures that the guidance relates to, to the beginning of the section	29.1-29.8, p 27-28 We will position the Figures at the start of this section for the final draft, thanks for the suggestion.
	Notes – these could go in a box as the paediatric notes have	30.4, p 29-30 Done.
	'…maker(paediatric…' change to '… maker (paediatric…'	30.28, p 32 Thank you.
Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI)	The terminology 'course correction' is nicely put. This implementation of this paper will need to address political sensitivities around this subject area. It will also mean that NHS Trust guidance will need to be updated, with the training implications that this has. Has implementation been addressed?	28.1 Thank you. We will need the support and involvement of the Stakeholder Group for implementation. We are in close contact with both NHS(E) and NICE as well, and will approach HEE to seek their interest in developing an educational module.
National Outreach Forum	We are pleased to see the use of NEWS/NEWS2 as the measure of acuity/severity although think that the treatment algorithm is too complicated and has the potential to very quickly introduce long delays in the treatment of sepsis or indeed, acute deterioration for other reasons.	Overall The working group has piloted this informally with senior trainees and the view we have received is that the frameworks follow current clinical thought processes and do not add additional burdens. But the acid test will be when the guidance is audited. It is difficult to see how the frameworks could be made simpler without loss of detail – and some other stakeholders have asked for more detail. We hope that with familiarity the frameworks will be found to work well.
Royal College of Nursing (RCN)	Suggest changing 'medical review' to 'Review within 30 mins by clinician competent in acute illness assessment' as stated in Figure 4.	29.5 Done

	Suggest separate section on 'Time to antimicrobial administration' for clarity.	Difficult with existing layout. We hope that once the guidance is adopted the various stakeholders will work together to create a better display for use by Trusts.
Paediatric Critical Care Society (PCCS)	PCCS acknowledges the potential utility of the national PEWS system (and indeed refers to it in the 6th edition of its recently published Standards). However, as far as it is aware, it has not yet been nationally rolled out but is being piloted in some centres alongside 1-2 networks.	27, P26 The SPOT programme is now referenced in the text.
	Section 30.3 states that the '*proposed frameworks are evaluated to determine their clinical utility*'. This AoMRC's position paper is rightly critical of the evidence base underpinning the Surviving Sepsis campaign and other related historical guidance. While PCCS fully supports the suggested 'course correction' there is no specific evidence base to support the proposed frameworks. PCCS therefore feels that there is an opportunity in section 30.3 to be more explicit about what research should be carried (and by which bodies) to provide the evidence base for the core recommendations going forward.	30.3, P29 We have added a few sentences on study design – cluster randomised or step wedge for interventions, and realist evaluation to examine 'what works, for whom, and why' in terms of the new guidance.
System wide Paediatric Observation Tracking (SPOT) programme	The SPOT programme are working to improve and standardise mechanisms to respond to deterioration across all locations where children and young people are assessed. The initial part of this work is to produce a national PEWS score and chart with associated system processes for inpatient use. A copy of the current version of this chart is attached, including the relevant escalation parameters. There is clear synergy between the proposed process as described in 29.3 and figure 5 of the AoMRC document with no conflict other than a slightly prompter review time in the PEWS escalation approach. We don't see this of being a problem with roll out of the AoMRCs approach.	Thank you. We have harmonised, but use ≥9 as our ceiling rather than adding the ≥13 PEWS band.
	The SPOT Oversight Team includes professionals (doctors and nurses) from a variety of specialties (from Intensive care to Emergency Department clinicians). One of the principles underpinning the development of a standardised PEWS system has been the objective to reduce missed opportunities to prevent all-cause morbidity and mortality. While Sepsis is clearly an important issue, deaths from asthma and trauma are also higher than	We agree. This is why our decision support framework, like SPOT/PEWS, starts with generic measures of severity and stabilisation.

	expected causes of death in children and young people in the UK compared to other European countries. It is for this reason that the advice on the chart is very generic as it is acknowledged the chart itself cannot be a complete guide to sepsis response. We would therefore value the AoMRC groups opinion on the list of conditions within the chart which we believe clinicians should use to think about whether Sepsis is present. It is going to be unlikely, especially for those sites using paper charts, that we will be able to embed specific information from figure 5 into the chart. Our hope would be that hospitals begin to embed the AoMRC guidance into their local sepsis protocols.	
	As noted previously the initial phase of the SPOT Programme of work was to derive an inpatient score and chart. Work starts in 2022 on Emergency Department, pre-hospital and community approaches. As you may be aware evidence is more mixed on Sepsis Screening in Emergency Department [1,2] and there is a very delicate balance between ensuring prompt review without creating decision fatigue with poorly specific systems. A standardised PEWS system may be a useful adjunct [3], together with the prompt to consider sepsis. Some SPOT pilot sites are evaluating the use of the PEWS score in an emergency department setting as well as in their inpatient wards. However, this is not a mandated requirement and it is likely an aligned system will be utilised in the first instance. The current AoMRC suggested divisions should allow flexibility for units managing children with a febrile tachycardia to be observed without a compunction for immediate intervention. At this stage we do not know how the ED and Pre-Hospital aligned scores will evolve but will be mindful of the AoMRC work.	We agree with this, but all the studies are in agreement that using NICE sepsis screening results in a significant number of false positives and overtreatment, and senior review of children who do not require it. AoMRCs guidance will also be reviewed and modified as evidence accumulates.
Royal College of Paediatrics and Child Health	Although active testing is currently taking place in pilot sites as part of the NHSEI SPOT Programme, drawing parallels between NEWS and PEWS would not be advisable at this stage. The national PEWS framework is yet to be clearly defined pending analysis and learning from pilot sites and current tools used to define the primary outcome are varied in their reliability and use. The Clinical Decision Support Framework [Figure	We understand this, and while the PEWS framework is yet to be clearly defined, there are compelling data from large ED studies to suggest that the NICE risk stratification results in overtreatment of children. We have added text and references to the section on paediatric severity scoring.

	5) should be more aligned to existing NICE risk stratification tools to prevent further confusion.	
Department of Health and Social Care	Well written to reflect sensitivities of this subject.	28.1
	Could guidance include specifics on what circumstances are required for 'Time Zero' to be declared to practically enable recording, informed decision making etc. Could 'Time Zero' be declared in a person's home, in an ambulance, or would it be declared in a hospital?	29.8 We have added some further explanatory text to para 29.8 and 29.9
	Really helpful structure for aiding clinical judgement – ensuring accessibility for junior doctors, nurses and community health workers could be useful to successful implementation of the framework.	30.4 Thank you.
	Overall, in terms of timings of the new framework, there seems to be an appropriate balance. Both rapid assessment and treatment of sepsis when it is needed and providing space for clinical judgement which supports optimal use of antimicrobials should be accounted for.	Thank you.
	Should differences in age groups be reflected in a more nuanced way? Neonatal sepsis, young children, children, young adults etc.	Our paediatric group were content with the current layout which maps well to the national PEWS programme SPOT. We agree than neonatal sepsis deserves a specific focus, but lies outside this remit at present. There is age-associated variation in physiological variables from birth to adulthood. Physiological compensation for serious illness is limited in children, so time is limited for staff or parents to recognise the signs and to respond quickly, to avoid the progression of deterioration to critical states [Sefton 2019]

General comments		
Organisation	**Comments**	**Page and para / response**
Intensive Care Society	I welcome this. 'Sepsis' does not exist as an entity (note three previous definitions), and as a concept was first produced to simply highlight those at greatest risk of deterioration. This document helps revert to that role. b. I support interventions which prevent blanket widespread unthinking use of antibiotics: society loses (AMR) as does the individual (increasing recognition of the long term harm caused by damage to the gut microbiome). c. Emphasis on use of NEWS to identify an enriched 'risk' population, and then a focus on 'clinical diagnosis of those with likely life-threatening bacterial infection' is welcome (as, at the moment, severe CCF, viral/pollution-triggered COPD and asthma can all trigger a use of antibiotics). This looks a well written document. I would support ICS endorsement.	Thank you.
ICUsteps	What is the status of specialist organisation guidance, such as this, when NICE guidance on the same topic exists? Is it up to local trusts to decide which guidance to follow? We recognise this guidance is about the initial treatment, but it is important that patients and relatives are provided with information and it would be helpful to have this included: — For those deemed not to have sepsis, safety netting about red flags and when to seek help if their symptoms progress (as sepsis can be missed) — What information is given to patients during this initial management stage — For those with sepsis which led to ICU care, information about what happened to them and what to expect/what will help their recovery. Information on our website www.icusteps.org/information, on UK Sepsis Trust website and others. Important to signpost to good quality information. Also important that patients receive information about delirium as they may have experienced that – information sheet on our website.	We are grateful to ICUSteps for having joined the working group, and to the Charity for this helpful feedback. We will co-produce a lay summary which will be the first section of the final position statement (draft currently in place) We will also co-produce an information sheet for patients and relatives to cover the points you raise here.

Infection in Critical Care Quality Improvement Programme (PHE)	The main concern for the paper is the methodology used. This is essentially a clinical practice guideline but does not follow published standards usually required in such a process. There is clear guidance in the literature about how recommendations for clinical practice should be formulated and drafted. The result of this is that the recommendations provide the reader with no qualitative descriptors describing strength of recommendation or quality of evidence. In many aspects the paper is more like an opinion piece rather than a formal assessment of the literature. It would benefit from having more balance. This is essentially a narrative review and does not describe how the evidence chosen was identified, evaluated or assessed. This is a limitation of the article and as such limits interpretation of its findings. This is especially important when combined with the lack of a conflict-of-interest policy. The methodology seems to be a modified type of Delphi process. There is no description of how consensus was built and what consensus meant. Is it all authors agreeing to everything or just a percentage of authors? Did each author vote at each stage and how as this handled?	This is an Academy Position Statement which offers a multiprofessional consensus combining a synthesis of the literature, broad clinical expertise, iterative discussion, and extensive stakeholder review. Where available we have used systematic reviews and clinical practice guidelines to guide our judgements. Where we offer different interpretations of the literature we explain the reasons in the report. The process is well-used by others, for example the ACEP policy statement on early care of adults with sepsis [Yealy 2021], the ISDA's recommended revisions to SEP-1 [Rhee 2020], and the IDSA's position statement on the Surviving Sepsis Campaign guidelines [IDSA Sepsis Task Force 2017]. Consensus means that all members of the working group (100%) approved the final document and the content of the frameworks. Consensus was attained through iterative discussion over 18 months. We did not use a Delphi process – the exercise was closer to a nominal group but without formal voting.
	There is no conflicts of interest policy described. This is particularly important for such a narrative review. It would be helpful to understand how financial and academic conflicts of interest have been handled. Often the academic conflicts (i.e., pre-conceived biases and views) are the most difficult to handle, with other similar 'policy-generating' articles now being very careful that authors with strong pre-conceived views or strong publication records / grant holdings in related subjects not being permitted to have strong inputs into narrative drafting and decision-making processes.	Competing Interest declarations will be included for working group members and stakeholder contributors. They will be provided in the next draft. We strongly agree about the importance of this [Bion 2018].

	The output of the paper is a decision support tool, which is similar to what international guidelines currently recommend although more complex. There is little description of how the tool was developed or what else was considered. Why have the authors chosen the metrics they did over and above others? There is no validation supporting the framework for the tool and the added complexity may make it less feasible to implement and runs the risk of confusing readers.	We thought that the totality of the report provided the rationale for the clinical decision support frameworks. We could provide earlier iterations of the frameworks but to liitle advantage. We have added addional information in this revision on the NEWS bands, partly in response to the comments from the UKST above. We propose research evaluation of the frameworks.
	There is a long list of reasons why the authors suggest rapid administration of antibiotics to life threatening conditions is not required. There is probably an equally long list of reasons why many groups would advocate for such a course of action. The manuscript only seems to give one side of the story and hence is likely to mis-lead or confuse the readers.	The reasons given by those promoting rapid administration of antimicrobials are already in the public domain and are the stimulus for providing this modest 'course adjustment' as we describe it. Moreover, the main difference between this AoMRCs guidance and that of groups such as the SSC is that we propose establishing treatment urgency on the basis of a generic measure of severity of illness. We also state that this proposal needs to be subject to independent research evaluation.
	The manuscript seems to be very against evidence-based guidance and guideline development (either from the Surviving Sepsis Campaign or the NICE). Discussing the limitations of EBM is one thing, being against it seems counter-intuitive. Why is this narrative and informal assessment of the literature any better than a formal approach? Perhaps a limitations section may be helpful pulling some of these issues out. The manuscript contains a lot of text describing the shortcomings of the Surviving Sepsis Campaign and their guidelines. It is unclear what the purpose of this critique is for a paper like this. It is worth noting that the current edition of the SSC guidelines has been supported and endorsed by all international societies who advocate in this area including the ATS, the IDSA, ESCMID, ANZICS, ESICM, , SCCM and ACEP.	We are surprised and concerned by this interpretation. In re-reading paras 2.1 to 2.5, we cannot identify any statement which is hostile to the SSC or to NICE. We do offer a critique of both, including the recognition of the weak evidence base and weak level recommendations.We entirely agree that others may wish to critique this position statement – which is why we recommend research evaluation. We should perhaps point out that Julian Bion was closely involved with setting up and supporting the SSC from inception and participated in the 2008 and 2010 guidelines, and was indeed an early proponent of mandating antimicrobials within one hour to patients with sepsis and organ dysfunction. We have had a very positive meeting with NICE and it is likely that they will convene a guideline

		group to examine more recent evidence on NEWS in sepsis and on timing of antimicrobials.
	The manuscript seems to misunderstand the use of performance metrics and how they are developed. The USA metrics are described as 'financial performance metrics.' This is not really the case. A more in depth understanding and explanation of quality and performance improvement may help the readers. Reporting of performance metrics, especially when combined with financial levers, has many limitations. The flip side to this, though, is that the prevailing scientific evidence supports the methodology in being associated with improved outcomes and reduced deaths. Although this has some methodological concerns, the use of evidence-based tools to improve quality is not inappropriate and positioning against them in such an article needs to be evidence based and with a sound rationale.	We are very content to be instructed on performance metrics if we have made errors in the report. We recognise (and one of us at least (JB) has published on) the complex relationship between performance metrics and clinician behaviour [Dixon-Woods 2012]. SEP-1 in the USA has been variously associated with improvements in outcomes [Townsend 2021], no improvements in outcomes [Barbash 2021] [Rhee 2021], and an increase in the unnecessary use of antimicrobials [Miller 2020]. There seems to be confusion in the USA as to whether SEP-1 is linked to financial reimbursement (Yes = Miller 2020 , No = Gesten 2021). We are therefore content to remove the word 'financial' preceding 'performance metrics' as it does not alter the main thrust of our argument, which is that performance targets can have both desirable and undesirable consequences.
Royal College of Physicians (RCP)	The RCP is grateful for the opportunity to respond to the above position statement. In doing so, we would like to endorse the responses submitted by the British Infection Association and the Nottingham University Hospitals NHS Trust Sepsis Action Group. We have also liaised with our Sepsis Lead, and our Clinical Director for quality improvement and patient safety and would like to comment as follows: This is a comprehensive document that outlines many aspects of the clinical care of patients with possible Sepsis. The focus on a balanced evidence-based approach to the timing and specificity of antibiotic use is welcome.	Thank you.
	The comprehensive nature of the background information, and evidence to support the guidance is helpful information but because it is so extensive may detract from the most important messages and	Our plan is to produce a (much) shorter version for peer-reviewed publication. Would that be OK? We chose the current layout because it 'tells a story', but we do understand

	conclusion of the working group. Some consideration should be given to a shorter form summary report, and then a full report, or whether some information can be moved into appendices, for example the workings of the group are not pertinent to the guidance for most readers.	that few people have time to read the whiole thing. We have written an executive summary, and will also provide a lay summary.
	The authors should consider the use of published rather than personal communication in 11.2 and figure 11.3 e.g. Pan D, Hills G, Hamilton AR et al. Recommended antimicrobial therapy for common inpatient infections: a comparative review of guidelines across 51 hospital trusts in England. Postgraduate Medical Journal 2020. In this study, guidelines published on Microguide were collected for the seven most common inpatient infections, including sepsis of unknown origin from December 2017-February 2018 and re-evaluated between December 2019- February 2020.	11.2: Thank you for this useful reference. We have included it in this section.
	The emphasis on treatment being guided by severity of illness is also welcome, and whilst evidence is strong for NEWS2 being a good measure of this, this must be used as part of an overall clinical assessment and not in isolation. In addition, some other measures of severity may be considered in specific presentations e.g. increasing oxygen requirements, hyperglyaemia etc. In practice in emergency departments NEWS2 score prompts rapidity and seniority of clinical assessment, and then other actions are informed by the clinical assessment including NEWS2 and other measures.	We entirely agree about avoiding reliance on any one measure. The decision support framework encourages a broad perspective (eg: second and third rows focus on clinical and lab assessment). We also agree (as does the science) that change in NEWS is important. We emphasise this in the second row by referring to 'continuing deterioration' as a criterion for upgrading actions to the next NEWS band even if this were not reflected in the physiology – which it probably would be anyway.
	High clinical suspicion of infection should enable treatment without delay The ability to "upgrade status to next severity band" appears arbitrary. As written, the algorithm appears to suggest treatment can be delayed up to 6h based on physiological score alone.	We are not proposing a delay. We simply state that the current evidence does not support the contention that patients who have an infection without organ dysfunction, or infection with organ dysfunction short of septic shock, require antimicrobials within one hour, or even three hours. In para 29.7, we state "*For the avoidance of doubt, it should be emphasised that these time frames are indicative: if actions can be completed earlier than the proposed time limit, then they should be. The time frames are not*

		intended to permit delay in treatment, but to offer the clinician time to make a safe and informed clinical decision"....
	We recommend it would be more appropriate for the severity band to be confirmed or stated following clinical assessment, thereby allowing for more flexibility for individual patients. This would be helped if the bands were 'named', and the most appropriate band after clinical assessment can be documented and communicated by the clinical decision maker.	The attending clinician can of course check the NEWS again following clinical review, and indeed we propose that this should be done as a routine within a specific time period. We have colour-coded the bands rather than name them, as we recommend research evaluation of these frameworks and it is therefore possible that the time intervals could be amended. At this stage we would prefer to retain NEWS as a 'common language' for severity combined with other measures and probability of sepsis, this being communicated through a standard tool such as SBAR.
	Probability of infection may be the most important part of the clinical assessment to guide treatment timing and specificity. Currently this appears to be separated from the assessment of comorbidities, whereas in practice these both occur as part of clinical assessment.	We are not proposing that experienced clinical staff should not condense activities into a single clinical examination. The framework cannot do that without loss of clarity however. And 'likelihood of infection' is part of the diagnostic phase, so logically must follow assessment, not precede it.
	We also welcome the importance of patient preferences in determining the intensity of treatment.	Absolutely.
	NEWS2 is now consistently used by ambulance services in England, and increasingly in other community-based assessments. This can change between presentation outside hospital and assessment on arrival at hospital, particularly with the institution of some treatments. In addition, the patient's condition can deteriorate after arrival in hospital. We therefore recommend that the highest NEWS2 during that presentation is used as part of severity assessment rather than only the NEWS2 score on initial assessment in on hospital arrival.	We acknowledge in the text that change in NEWS adds value to the prediction of outcome. This is implicit in the reference to 'deterioration' in the assessment framework, and we have emphasised it in the introduction to the frameworks (section 29) with the following text: "*They are dynamic instruments designed to permit upgrading or downgrading of priorities and treatments according to the patient's condition*" and elsewhere in this section.
	The time frame from hospital presentation to antibiotic treatment initiation is appropriate as described, with this timing	Thanks – pleased you agree.

	starting on hospital arrival, as this then gives relevant time frames for other elements of clinical assessment that may lead to more targeted treatments.	
	We do not find the Clinical Decision Framework intuitive. We recommend that the framework is adjusted in line with clinical workflows and decision making, therefore making it more in the format of a decision tree. The initial monitoring plan comes immediately after the initial NEWS 2 score, and therefore should be the second row. This is followed by clinical assessment which considers differential and working diagnoses, including critical diagnoses, evidence of organ dysfunction, co morbidities including frailty, and clinical likelihood of infection. The 5th row information is duplicated in the section related to probability of infection and should therefore be removed. Therefore, the initial NEWS2 score will determine the time to initial and seniority of clinical assessment. This should then lead to a clinical assessment of the likely hood of infection. This will then determine the time to initiation of treatment and other strategies. As above we recommend that the treatment columns are named, to enable some flexibility based on overall clinical assessment.	We have tried the format you suggest but this then raises other complexities. In any case, the framework will need piloting, modifying, formatting and development which we hope will be undertaken by professional bodies such as the RCP and locally by NHS Trusts. A flow diagram could certinaly be one such outcome. We hope that the RCP and other organisations will offer their skills to this end. The framework is intended to offer a preliminary logic model which runs thus: 1. Is this patient sick? [NEWS] 2. Assessment: i) What other severity of illness factors in addition to NEWS do I need to consider? ii) Are there any background health/non-acute factors which may affect either urgency or goals and limits of treatment? 3. What immediate actions are needed to assure patient safety? i) Monitoring & escalation plan ii) Generic actions: Initial stabilisation & treatment 4. What is the underlying cause? Is it infection? What are the goals of treatment and timelines for sepsis? We have added this explanatory text to section 29.1
	There are some statements in the report which are opinion, and should either be reworded to make that clear or referenced, e.g. page 9 5.1 *Clinicians must therefore act*	We have qualified the phrase 'it is easier' with the addition of 'may'.

	under uncertainty, but are judged with hindsight, and usually on the basis of process audit rather than patient outcomes. Consequently, in the pressured environment of emergency care, it is easier to give antimicrobials to patients who might be septic than to justify delay while refining the diagnosis. Paragraph 29.2 would benefit from some rewording; it is unclear what 'point of entry' means.	29.2 and this section have been extensively reworked.
Royal College of General Practitioners (RCGP)	In relation to the paper itself, the RCGP recognises that this is a significant piece of work with it's focus on secondary care. It would be beneficial to either highlight this secondary care focus in the introduction, or if the aim was to cover the whole pathway, to add a specific section that relates to primary care. This is important as primary care continues to use a clinical review alongside the NICE guidance pathway and is not mandated to use NEWS 2/ PEWS. I am sure Simon highlighted the RCGP council position (2020) on "Sepsis and the use of NEWS score for assessment of deteriorating patents" (attached) the recommendations from which are below — The RCGP recommends the use of physiological measurements when assessing patients at risk of deterioration in primary care — The RCGP recommends that on requesting a level 2 emergency ambulance dispatch for patients (16 and over who are not pregnant), clinicians should, when possible, provide appropriate physiological measurements to the ambulance switchboard operator and paramedics upon arrival — The RCGP does not recommend the use of NEWS2 as a replacement for clinical judgement — The RCGP recognises that some areas and GPs currently use NEWS2 when assessing their patients and arranging their admission. This should be viewed as optional and ideally should be done as part of a governed system where its value to patient safety and care is being assessed	We are unable to convert the entire report into a secondary care statement because we must encompass the whole of the patient pathway, and primary care is crucial in that respect. In 6.18.3 we referenced Burns et al's letter in reply to Inada-Kim et al pointing out that pre-test probabilities may influence the utility of NEWS-2 as a measure of severity of sepsis in primary care, but even with this caveat there is still an impressive link between primary care NEWS-2 and subsequent mortality. As far as the practical use of NEWS is concerned, we do emphasise that this is a clinical decision support framework, and repeat several times that we are trying to restore clinician judgement in patient care. So the 5 bullet points are all consonant with the current document. I have added the following text to para 2.18.2: "*The Royal College of General Practitioners Guidance [RCGP 2020] recommends the use of physiological measurements when assessing patients at risk of deterioration in primary care as an adjunct to [not as a replacement for] clinical judgement and recommends further research on the use of NEWS-2 in this setting*".

	— The RCGP recommends further research on the use of NEWS2 in General Practice to validate its use in this setting Our particular concern is therefore, unless it is highlighted that this report focuses on the secondary care pathway of sepsis is that point 6.18.2 could be read as supporting the unevidenced use of NEWS 2 in primary care, so would also request acknowledgement of the RCGP position as above. Unfortunately, without acknowledging our college policy in this area, it would be difficult for us to support the report as it stands.	
South-West Critical Care Network	I welcome the group's attempt to simplify such a complex issue of sepsis and antibiotic stewardship, and I couldn't agree more with the last highlighted sentence below (quote from the document) **30.5** *NEWS-2 should be used in conjunction with clinical assessment, not to replace clinical judgement.* What is interesting is that the position statement criticises the papers regarding early antibiotics of being retrospective (which I fully agree) and currently used biomarkers are non-specific for bacterial infection/sepsis, however they are pushing for NEWS-2 in the over 16y which to my knowledge also not based on RCTs and impact on outcome studies. We need to exercise caution when/ if these recommendations are adopted as NEWS itself can be not specific / sensitive . A large European multi-centre study (~2000 patients again retrospective) demonstrated that NEWS < 5 can be falsely reassuring and clinical context including biomarkers can be incorporated to decision making and recognising deteriorating patients. In the statement itself (18.2) they suggest "Immunosuppressed or elderly patients may not develop fever, leukocytosis or tachycardia, while younger patients may not present with typical features of physiological deterioration until very late ", hence putting such emphasis on NEWS-2 in the rest of the guidance is not scientifically justified. Look at figure 4 in [Saeed 2019]	We are not sure that 'pushing' is quite the right term. As we state in para 25.1, NHS England mandated NEWS2 national implementation across all hospital and ambulance trusts in 2018 [NHS England], and is strongly endorsed by the Royal College of Physicians. As it has been adopted across the nation and is now in use in other countries, it would be unwise not to propose it as the preferred instrument for initial assessment of the acutely ill patient. We agree that it would benefit from prospective research, and we provide references to articles which offer retrospective analyses of prospectively collected data. We have added to para 25.3 the following statement: *Caution is required however, when applying any of the Early Warning Scores to specific (and usually single-organ) disease states [Alhmoud 2021]; recalibration may be required for Covid-19 [Richardson 2021] [Baker 2021]*. We have also referred to Saeed 2019 in the NEWS section and in the biomarker section 201. Thank you.

	and Figure S8 (in its supplementary files). Clearly having same NEWS-2 numbers for someone who is 17 vs 59 vs 85 Y, pneumococcal pneumonia doesn't have the same outcome in these groups even without comorbidities. I think is time to do RCTs for these clinical scoring systems (NEWS 2) with and without biomarkers to have a better and well informed decisions. The document need to make this absolutely clear that clinicians decision could override the NEWS-2 value, as to external non clinician regulators these documents can be taken very prescriptively, and undoubtedly will be used for external monitoring, compliance and quality checks and benchmarks. I know it is mentioned but I think the document should make it even clearer that clinicians should not be disempowered to make their own decisions and override these statements.	We have emphasised the importance of clinical judgement in 29.7.
UK Sepsis Trust	Thank you for the opportunity to review this helpful document. We welcome initiatives which focus on improving outcomes from sepsis whilst minimising antimicrobial resistance. We welcome the use of NEWS2 (and similarly designed paediatric and maternal aggregate track-and-trigger scores) as a baseline to prompt suspicion of timedependent infection and sepsis in patients presenting with suspected or confirmed infection. Further, we understand and see as reasonable the use of graded thresholds of (e.g.) NEWS2 to guide rapidity of intervention and escalation. This is of course in keeping with the recent revision of the Surviving Sepsis Campaign guidelines particularly with relation to timing of antimicrobials, in which a more generous 3-hour window is suggested for administration in patients with the absence of shock and in whom the diagnosis is less clear. We absolutely acknowledge and agree that evidence in support of antibiotics within 1 hour for ALL patients with sepsis (including without shock) is not compelling. We would like the opportunity to offer the following general feedback following our review:	Thank you. To respond to point 1, the delay in consultant review of emergency admissions to which you refer does not necessarily indicate inferior care. It could be interpreted as an argument to address the concern you raise and for the position we currently adopt, that scarce resources need to be focused on patients most likely to benefit. We agree that patients may have a serious or life-threatening illness despite a low presenting NEWS, and for this reason provide three security measures: i) that clinical judgement should override the algorithm; ii) that at the lowest NEWS (1-4) patients must be reviewed within one hour, and the frequency of observations should be increased if the patient is not improving and iii) the time limits are maxima – we state in the text that actions should be completed in as timely a manner as possible (29.7).

	1. Operationally within a resource-constrained NHS, we are seriously concerned about the safety of extending the window for antimicrobial administration to 3 and 6 hours in individuals with lower NEWS2 scores. All too frequently, contact between patient and prescribing clinician occurs at or near presentation and following this at the post-take ward round the following morning. We have seen self-reporting against Standard 2 of the NHS England Seven Day Clinical Services Standards (2017), noting that in some regions only 1 in 8 emergency admission patients is reviewed by a consultant within 14 hours. In implementing the proposed recommendations, unless organisations specifically design systems which mitigate against extensive delays for this cohort of patients, then we feel it inevitable that harm will arise 2. The discussion of sepsis incidence within the document would offer, in our view, better balance and discussion if were to include acknowledgment that the estimates concluded place the incidence of sepsis far lower than that reported in any international point prevalence study or epidemiological study 3. Appraisal of the literature in relation to timing of antimicrobials is clearly important: the paper would be enhanced if a systematic review approach had been favoured. We note omissions from the current narrative review, e.g., evidence against the author's narrative from Johnston ANB (Clin Ther 2017) and from the Surviving Sepsis Campaign (Intensive Care Med, 2010) 4. Due consideration could be afforded within this document to its position with respect to alternative guidance from NICE and from the Surviving Sepsis Campaign, the latter updated only last month. The methodologies of the NICE and SSC approach are clear and pre-specified which adds value to their outcomes 5. This paper would (in our view) be enhanced if it were to include an analysis of intended benefit, in terms of individual patient benefit and estimated reductions in antimicrobial consumption, as well as of	Point 2: we have corrected the error in our previous draft relating to the incidence of sepsis in England. Point 3: We have made use of the articles referred to in the Surviving Sepsis Campaign guidance (we believe you mean the 2021 publication, not 2010) and from other systematic reviews and trials which we reference in paras 14.1 and 14.2. Point 4: We have had a very positive discussion with NICE who are willing to consider revising their current guidance on both sepsis and acute deterioration in the light of new research. Point 5: We agree that this would indeed be of interest and have added health economics to the section on research evaluation.

	possible unintended consequences and risks	
	As an organisation active in advocacy as well as the provision of pragmatic, operational resources to organisations and to junior health professionals, it is essential that any output we support is practical, operationally deliverable and patient-centred. As such, we cannot ratify or endorse guidance which has been developed without patient or "end user" (in this case junior doctors and nursing staff) input. The UKST have a proven track record in the operationalisation of such guidance (e.g., NICE) which has proven popular in the NHS and further afield. We would happily utilise UKST's skills, patient and professional network to support the translation of this AoMRC guidance into such operational guidance and toolkits. Should working together on this be of interest to the Academy then I would be delighted to discuss.	Thank you. We note these comments. The development of this position statement by professional and scientific organisations will be coordinated by the Academy of Medical Royal Colleges, and we anticipate that NICE will convene a guideline group to examine the new evidence which has emerged since the last NICE guidelines on sepsis.
	As an organisation active in advocacy as well as the provision of pragmatic, operational resources to organisations and to junior health professionals, it is essential that any output we support is practical, operationally deliverable and patient-centred. As such, we would require detail around the level of involvement of patients or people with lived experience, and of junior doctors and nursing staff, in the process prior to supporting. Evidence of the cited field testing would be extremely helpful in this regard. The UKST have a proven track record in the operationalisation of such guidance (e.g., NICE) which has proven popular in the NHS and further afield. We would happily apply UKST's skills, patient and professional network to support the translation of this AoMRC guidance into such operational guidance and toolkits. Should working together on this be of interest to the Academy then we would be delighted to discus	See responses above and elsewhere.

West Midlands Adult Critical Care Network	Table of contents – figures and tables, appendices – all incomplete	2 The draft will be subject to final editing.
	Should this include a table for PEWS similar to the one for NEWS?	56 As soon as the SPOT programme release their age-adapted versions of PEWS we will provide the reference.
NHS England and Improvement Professional & System Leadership - Community Nursing	Would be useful to highlight the need for a standardised training pack for awareness and detection of sepsis to accompany this work – also patient / carer information for detection of that community nurses can share.	We have added to 7.3.1 a note that the frameworks can be used and developed by a wide range of organisations, including those responsible for training.
Scottish Anti-microbial prescribing Group (SAPG)	In general the document was well received and supported – particularly the nuanced approach towards management based on NEWS 2 and likelihood of infection. There will be practicalities regarding infection specialist input during the empiric phase of therapy and some compromise to this has been suggested based on clinical uncertainty and severity of infection.	
	In SAPG there is significant concern and focus of review of the antimicrobial/infection management plan to minimise unnecessary antibiotics. We are therefore keen to promote early IVOST and shorter duration therapy whenever possible particularly when there has been time for a clinical response and for culture results are available. As such a specific 72 hour review might be captured within an additional line at the bottom of table – this would also dove tail with our SAPG Hospital Antibiotic Review Programme	We have changed the time period for antimicrobial review to 48-72hrs. We hope this is agreeable.
	There is no reference to COVID-19 in the document. This is important as Sepsis and severe COVID-19 may be confused and diagnosis of sepsis may be challenging in the context of COVID-19.	We have now included COVID-19 in paras 10.2, 19.1, 20.1, and 25.3
	More specific comments of the risk matrix itself: 1. ***Additional concerns and comorbid disease*** – think these are useful additions. 2. ***Generic actions*** – agree 3. ***Clinical likelihood of infection "Unlikely": Review 24-hourly "for risk of infection tests"*** – not clear what this means – Should this be "review daily	3. Thank you. Modifed to: "*Review daily and reconsider infection if diagnosis remains uncertain*"

	and reconsider infection if diagnosis remains uncertain" 4. ***Clinical likelihood of infection "Possible":*** divisions between NEWS-2 0 and 1-4 are artificial so should be merged: "within 6 hours: microbiology tests, source identification and control plan. Consider antimicrobials [administer, revise or defer] based on clinical scenario" 5. ***Clinical likelihood of infection "Probable or definite":*** suggest remove the NEWS 0 box and merge with NEWS-2 1-4 – no change to the text in NEWS-2 1-4 6. D/w Infection specialist if uncertain could be pasted in all the boxes for Possible or probable/definite irrespective of NEWS. However should also mention following guidelines regarding required investigations. 7. ***NEWS 5-6: Within 48 hrs - Review antimicrobials*** – suggest remove reference to ID/Micro as empirical guidelines provide advice and IV to oral switch options. If any blood cultures are positive, ID/Micro will contact the team. If the patient is not improving with empirical treatment after 48-72 hours then appropriate to contact an infection specialist. 8. ***NEWS >=7: with 24 hours – Review antimicrobials*** – suggest reference to micro/ID as above. Also suggest that reviewing within 24 hours is too soon and should be 48 hours as per 5-6 9. ***The review aspect of the guidance could be expanded***. Suggest that 48 hours is often too early to be definitive with an infection management plan. The bottom line of the table could be devoted to a 72 hour review for those with possible or probable/definitive infection– irrespective of initial NEWS-2 score. Suggest something like: — **72 hours** Review and document infection management plan — Review clinical response, laboratory and radiology results and consider source control — Consider IVOST/ Stop/ De-escalate / Infection specialist review — Record plan and limit duration of antimicrobial therapy per local guidance	4, 5 6. The NEWS2 band = 0 is a necessary component because we start with the question 'is this patient sick?', not 'is this patient septic?'. And the actions linked to likelihood of infection differ between 0 and 1-4. It might be that these can be merged following formal evaluation. 7. We do state 'if uncertain' which leaves room for following local or national guidance. 8-9. We have now extended the period to: 24-72 hrs. We are reluctant to overburden the diagram with text, but with research evlaution it will become clearer which elements need modifiying.

	10. Role of infection specialists – they should be more accessible in acute medical and surgical areas and able to provide consultation on all acute inpatient areas but appreciate difficult to describe within this matrix. Medical receiving units should have routine input from infection specialists to not only identify those who should go to a specific ID bed but also for stewardship issues.	

Endorsement		
Organisation	**Comments**	**Endorsement?**
Defence Medical Services	We support the guidance but will not formally endorse it as there are significant differences in how we practice medicine in the deployed military setting. Our provision of deployed healthcare differs significantly from the civilian sector with respect to senior review of patients in small primary and secondary care facilities and remote settings. The former typically offers patients an earlier senior review than an NHS setting, the latter typically a later review and could include prolonged patient stays outwith the time lines proposed - neither situation is considered in this document. Our attitude to forward provisioning of rapid laboratory diagnostics in certain (but not all) environments, for example Biofire multiplex PCR, affects diagnostic and treatment timelines compared to NHS equivalents. Our population is such that pre-existing comorbidities are less likely to be present in acute presentations of presumed sepsis, and our population's physiological fitness may affect NEWS-2 scoring. Our timeframes are typically operationally driven - so keeping to the time frames offered by this paper may not automatically match our clinical timelines. We are about to begin the process of reviewing our secondary care Clinical Guidelines for Operations and will take the AoMRC guidance into account when reviewing our military sepsis guidance.	Thank you for agreeing the following: "The Defence Medical Services does not endorse guidance or statements produced by civilian organisations, but currently holds broadly similar views to those expressed in this position statement".
Intensive Care Society		Yes subject to final review
ICUsteps		No response
Northern Ireland Intensive Care Society		Yes subject to final review
Royal College of Emergency Medicine		Yes pending usual processes
Royal College of Obstetricians and Gynaecologists		No response

Royal College of Physicians (RCP)		Yes
Royal College of Physicians of Edinburgh		Yes
NHS England and Improvement AMR Programme, including collated comments from the Acute Deterioration Board		Yes
NHS England and Improvement Professional & System Leadership - Community Nursing		Yes - supportive and would like to be involved in future work to link to patient safety work as part of the National Community Nursing Plan
UKCPA Critical Care Group		Yes
UK Clinical Pharmacy Association (UKCPA) Infection Committee		Yes
UK Sepsis Trust		
United Kingdom Health Security Agency		Yes, but will need to go through an internal process to do so
West Midlands Adult Critical Care Network		No response
Chartered Society of Physiotherapists (CSP)	No additional comments received on paper	Yes
Association of Chartered Physiotherapists in Respiratory Care	No additional comments received on paper	Yes
Association of Cardiothoracic Anaesthesia and Critical Care (ACTACC)		Yes
Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI)		Yes
National Outreach Forum		Yes
Royal College of Nursing (RCN)		Yes - The Royal College of Nursing is supportive of the position paper. We support the endorsement subject to amendments and clarifications that we have

		indicated above. We can confirm this once we receive the final version.
Paediatric Critical Care Society (PCCS)		Yes - PCCS is willing to endorse this document subject to clarification on the points raised.
Welsh Intensive Care Society (WICS)	No additional comments received on paper	Yes
Department of Health and Social Care	As agreed, DHSC endorsement will be sought in the New Year following advice to the Chief Medical Officer and relevant Minister.	