**National Institute for Health and Clinical Excellence**

**Diarrhoea and vomiting in children**
**Guideline Consultation Comments Table**
**14 October – 8 December 2008**

| Type | Stakeholder | Order No | Docu-ment | Section No | Page No | Comments<br>Please insert each new comment in a new row. | Developer's Response<br>Please respond to each comment |
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| PR | NCCHTA 1 | Q1 | Full | 1.1 | | Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached) | No response required |
| PR | NCCHTA 1 | Q2 | Full | 2.1 | | Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelines manual). | No response required |
| PR | NCCHTA 1 | Q2 | Full | 2.1 | | Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelines manual). | No response required |
| PR | NCCHTA 1 | Q4 | Full | 3.1 | | How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected? | No response required |
| PR | NCCHTA 1 | Q6 | Full | 4.2 | | Please comment on whether the research recommendations, if included, are clear and justified. | No response required |
| PR | NCCHTA 1 | | Full | 3.2 | | Are any important limitations of the evidence clearly described and discussed? | No response required |
| PR | NCCHTA 1 | | Full | 3.2 | | Are any important limitations of the evidence clearly described and discussed? | No response required |

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| PR | NCCHTA 1 | Q2 | Full | 2.1 | | Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelines manual). | No response required |
| PR | NCCHTA 1 | Q5 | Full | 4.1 | | Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence. | No response required |
| PR | NCCHTA 1 | Q3 | Full | 2.2 | | Please comment on the health economics and/or statistical issues depending on your area of expertise. | No response required |
| PR | NCCHTA 1 | 1 | Full | | | No comment | Thank you |
| PR | NCCHTA 1 | 2 | Full | 7.3 | 117 L13 | Throughout this report each section author has used differing study quality inclusion criteria. In each case I recommend that a central (lead) author reviews and is happy with each section. This lack of consistency between trying to collate strong evidence only using studies with greater than 100 participants (as exercised on page 50 (Line 2) compared to a section which has compromised robust conclusions because of having to include findings from extremely small samples exaggerated on Page 117 (Line 2) where four patients are compared in each arm. | The lead reviewer has examined both sections and is satisfied with the approaches taken across the guideline. The review team has tried to incorporate the best available evidence. At the same time they have successfully highlighted the methodological limitations of the available evidence. The GDG were also aware of these limitations as reflected in their translation of evidence. The small sized study (ref 145) with 4 children in each arm has been given an evidence level of 1-, and does not influence the recommendation.<br><br>Kindly also see our response to your |

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| | | | | | | | comment number 33 for clarification regarding introducing a minimum sample size. |
| PR | NCCHTA 1 | 3 | Full | General | | Q2<br>**Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).**<br>The inter-disciplinary team who put this guideline together would have benefited from the advice of a dedicated statistician. I recommend before this guideline is accepted the co-coordinating author ensures that the statistical content is correct and appropriate throughout this report. (including: the glossary, all meta analysis [with reference to I2], all statistical analysis (as carried out and reported in the original publications) and their interpretation. | Thank you. In light of your comment, the team has reviewed the statistical content in details, and made appropriate changes. |
| PR | NCCHTA 1 | 4 | Full | Glossary | 9 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Bias– This is too long and poorly described. Bias is a systematic difference between what has been measured/recorded and what the actual measurement is. | Thank you for your comment. Appropriate changes have been made. The definition that you have provided is of measurement error, not bias. |
| PR | NCCHTA 1 | 5 | Full | Glossary | 9 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Blinding is not the same as masking. See | Thank you for your comment although we disagree. This difference is used selectively only. |

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| | | | | | | "Selection bias and covariate imbalances in randomized clinical trials" by Vance Berger. | |
| PR | NCCHTA 1 | 6 | Full | Glossary | 9 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Case-control study – This is too long and poorly described. | Thank you for your comment.<br>Appropriate changes have been made. |
| PR | NCCHTA 1 | 7 | Full | Glossary | 9 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Causal relationship – This is too long and poorly described. Also note all other factors can not be ruled out, and in only some instances controlled. | Thank you for your comment. The term has been deleted as it is not in the text. |
| PR | NCCHTA 1 | 8 | Full | Glossary | 10 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Cluster – This definition should include why patients are defined as a group. "A group of patients with correlated responses used as the basic unit for investigation…" | Thank you. We disagree that the group has correlated responses.<br>Nevertheless the definition has been revised. |
| PR | NCCHTA 1 | 9 | Full | Glossary | 10 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Cluster design – This is not factually correct. For example there are many studies where the general practice implements individual patient randomized trials.<br>Also the current definition could be used to describe a patient randomized multi-centre trial. | Thank you. The term has been deleted as it is not in the text. |

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| PR | NCCHTA 1 | 10 | Full | Glossary | 10 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Cochrane Collaboration – This needs to be changed. The Cochrane Collaboration carries out systematic reviews consisting of many different types of studies including CBA, CCT, ITS, etc. RCTs are simply the 'gold standard' but not the only study they include. | Thank you this has been revised. |
| PR | NCCHTA 1 | 11 | Full | Glossary | 11 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Cohort Study – This is too long and poorly defined. | Thank you. This has been agreed and appropriate changes made. |
| PR | NCCHTA 1 | 12 | Full | Glossary | 11 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Co-morbidity – This is grammatically imprecise. | Thank you. This term has been removed |
| PR | NCCHTA 1 | 13 | Full | Glossary | 11 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Confidence interval – This is too long and I would warn against suggesting it uses "statistical techniques" since we are trying to make these guidelines transparent, rather than create a black box effect. | Thank you. We disagree with your comment. Statistical technique is a commonly used terminology and would be easily understood by the readers. |
| PR | NCCHTA 1 | 14 | Full | Glossary | 12 | | Thank you. This definition has been |

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| | | | | | | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br>Confounder or confounding factor –<br>"Something that influences a study and can contribute to misleading findings if it is not understood or appropriately dealt with" - This is not a reasonable definition see (Woodward 1999, Epidemiology) | revised. |
| PR | NCCHTA 1 | 15 | Full | Glossary | 13 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Cross over study. - This is too long and should inform the readership that patients are treated by all interventions/medications throughout the study. I also don't think its is appropriate for the authors state the cons of a study design, particularly if they neglect to education the readers about the pros i.e. a reduction in the total sample size required! | Thank you. The term has been deleted as it is not in the text. |
| PR | NCCHTA 1 | 16 | Full | Glossary | 13 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Data set – Is this required ? also note that a dataset doesn't need to be related to disease. | Thank you. The term has been deleted as it is not in the text. |
| PR | NCCHTA 1 | 17 | Full | Glossary | 13 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Diagnostic Study – These are studies that ensure reliability and repeatability, as well as | Thank you. The definition has been revised. |

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| | | | | | | test the effectiveness. Note: "Diagnostic Study" is not referenced within the guidance document. | |
| PR | NCCHTA 1 | 18 | Full | Glossary | 14 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Efficacy – Efficacy is demonstrated within the clinical environment and not just in the lab. | Thank you. This definition has been revised. |
| PR | NCCHTA 1 | 19 | Full | Glossary | 15 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Extrapolation – Please correct - see any basic introductory statistics text. The key is prediction 'outside' of the normal range of your empirical evidence. | Thank you. The term has been deleted as it is not in the text. |
| PR | NCCHTA 1 | 20 | Full | Glossary | 15 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Funnel Plot – I suggest you do not use the word 'simple' and highlight why they are used i.e. to assess the publication bias. Please note that the author does not reference "funnel plot" within this guidance document. | Thank you. The term has been deleted as it is not in the text. |
| PR | NCCHTA 1 | 21 | Full | Glossary | 16 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Heterogeneity & Homogeneity<br>Both definitions are inaccurate. Please see The Cochrane Handbook for an introductory definition (Feb 08). The key is that the variability within the studies are inconsistent and this has nothing to do with treatment effect. | Thank you. Both the definitions have been revised. |

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| PR | NCCHTA 1 | 22 | Full | Glossary | 18 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Meta analysis – The studies do not need to use the "same treatment", as this might be an intervention, or a similar type of generic formula of treatment, | Thank you for your comment with which we agree. The definition has been revised. |
| PR | NCCHTA 1 | 23 | Full | Glossary | 19 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Odds ratio – This is too long and imprecise. | Thank you. The definition has been revised. |
| PR | NCCHTA 1 | 24 | Full | Glossary | 21 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>P value - please simplify. I suggest that a robust definition is provided. | Thank you for your comment although we disagree and find the definition to be comprehensive and self explanatory. |
| PR | NCCHTA 1 | 25 | Full | Glossary | 22 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Random allocation - This definition should describe the allocation of units, rather than participants (think about cluster randomized studies). Also note that only in studies with a 1:1 ratio do the units have an equal chance of being allocated to either group. This term is not used within the main body of the text | Thank you for your comment with which we agree. Appropriate changes have been made. |
| PR | NCCHTA 1 | 26 | Full | Glossary | 23 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Selection bias – Provide a definition, rather than | Thank you for your comment although we disagree and find the given definition is scientific and precise and does not give an example. |

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| | | | | | | an example. See Burger V. as previously mentioned. | |
| PR | NCCHTA 1 | 27 | Full | 3.1 | 46 L42 Table 3.1 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Reference Szymanski 2005 [41] is listed in the references as a 2006 study. | Thank you. This error has been corrected. |
| PR | NCCHTA 1 | 28 | Full | 3.1 | 47 L16 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Line 16 – GDG has not been included within the glossary | Thank you. The term GDG and the composition of the group have been described in detail under section 1.6 (Who has developed the guideline?). Including it in the glossary would be repetitive. |
| PR | NCCHTA 1 | 29 | Full | 3.1 | 47 L1 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Table 3.2 – It would be helpful to describe ref 45 in a little more detail in the text. This table is a good summary. | Thank you. More details have been provided for the study (Ref 45). |
| PR | NCCHTA 1 | 30 | Full | 3.1 | 48 Table 3.2 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br>Please justify the "Overall" category. The author will confuse the audience with this, particularly as readers would use the "Overall Mean duration" unless they explain that it's a weighted mean duration. Where its weighted by number of patients from each study. However, others will argue you would want to weight only those with a higher quality status. Also correct | Thank you. Appropriate changes have been made. The total duration given in the study is the mean duration of the total sample and is not the weighted mean.<br><br>Thank you – the figure has been amended to 16% |

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| | | | | | | Salmonellae as 98/595 should be rounded to 16%. | |
| PR | NCCHTA 1 | 31 | Full | 3.1 | 49 L15 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Line 15, which 4 cross sectional studies 'indicate this'. This implies a meta analysis been confirmed to this effect, if so then please present the 95% CI. If not, please reword ensuring the guidelines reflect the evidence. | Thank you. The evidence summary has been revised to clarify this point. Meta-analysis has not been conducted in this section. |
| PR | NCCHTA 1 | 32 | Full | 3.1 | 49 L23 | again which cross sectional studies? if the studies reported these findings please reflect this in the text. If this result has been presented somewhere, please include the 95% CI. | See comment NCCHTA1 31<br>Thank you. The evidence summary has been revised to clarify this point. Meta-analysis has not been conducted in this section. |
| PR | NCCHTA 1 | 33 | Full | 3.1 | 50 L2 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Until now all literature reviews have captured studies with no minimum sample size. Why has this changed here ? A consistent approach within the report should be attempted where-ever possible. However, tables 3.1 and 3.2 both include multiple studies with less than 100 participants. | There were no comparative studies to inform this question on characteristics (signs & symptoms) of alternative diagnosis, and the best available studies were case series. Being an evidence-based guideline, it was decided to include these studies but improve the quality by pragmatically introducing a minimum sample size. The evidence was further supplemented by the NICE published guideline on 'Feverish illness in children' and the knowledge/ experience of the GDG members. This has been now made clearer in the text.<br><br>We disagree regarding consistency of approach. The methodology followed in |

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| | | | | | | | this guideline is robust and based on the NICE guidelines standard – see manual. It aims to look at the best available evidence.<br><br>Tables 3.1 and 3.2 are based on the information presented from different questions. They are not relevant for this question. |
| PR | NCCHTA 1 | 34 | Full | 3.2 | 52<br>L4-L6,<br>L45 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br>The HPA surveillance data is not from a random sample so has limited (if any) power for estimation of prevalence or generalisability. It can easily be argued that both many cases are not diagnosed and sent for analysis or only those of greater virulence are diagnosed. | Thank you. The GDG was well aware that the HPA data collection is not comprehensive. This fact is acknowledged on page 55, lines 7-8. Nevertheless HPA data is valuable. For example the surveillance study referred to on line 45 showed a difference in the responsible viral pathogens during the outbreak of gastroenteritis. The submitted data, although incomplete, identifies important trends. |
| PR | NCCHTA 1 | 35 | Full | 3.2 | 52<br>L25 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br>Please check the year the data was collected as it has been well publicized that Cryptospiradium and other resilient environment bourne bugs were less prevalence in the aftermath of the foot and month outbreak because of the countryside and environmental restrictions. | Thank you. The study (Ref 54) was conducted during 1986-87 and cannot be related to the foot and mouth outbreak. Kindly see the first sentence of the relevant paragraph for more information. |

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| PR | NCCHTA 1 | 36 | Full | 3.2 | 55 Table 3.4, Table 3.5 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Same as above, 2002 Crypto is low… | Thank you. The figures have been taken from the published evidence and HPA website. They cannot be changed. |
| PR | NCCHTA 1 | 37 | Full | 3.2 | 53 L11 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>How was "healthcare acquired" defined ? be careful over the sampling strategy carried out within the original work. | Thank you. It has already been defined in the text – 'gastroenteritis was considered to be health-care associated if symptoms developed ≥ 48 hours following admission'<br><br>Information about sampling strategy (consecutive, random) was not given by the study authors. |
| PR | NCCHTA 1 | 38 | Full | 4.1 | 62 L23-24 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise**<br>check references. | Thank you. |
| PR | NCCHTA 1 | 39 | Full | 4.1 | 62 L25 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>please note these evidence has been gathered predominately from Indian origin. | Thank you. The applicability of the evidence (risk factors) in UK setting has been adequately described under 'GDG translation from evidence to recommendations'. Kindly see the relevant section for more details. |
| PR | NCCHTA 1 | 40 | Full | 4.1 | 63 L9 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.** | Thank you. The typographical error has been corrected. |

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| | | | | | | Page 63, line 7, p-value should read 0.048 which does offer statistical evidence at the 5% level (line 9), as the 95% CI indicates also. | |
| PR | NCCHTA 1 | 41 | Full | 4.1 | 63<br>L24-L33 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Reference 71 – interpretation of the birth weight. This should be interpreted as babies < 2500g only are at an increased risk. I would suggest the authors revise lines 24 to 32, many of the statistical evidence exhibited. The publication describes that younger babies are of an increased risk and try not get too bogged down with the multiple univariate tests. However, an acknowledgement of the extent of the multiple testing would be useful. | This study reported a number of factors associated with an increased risk of dehydration. Excluding other factors (apart from low birth weight or <2500 gms) from the text would be methodologically incorrect. |
| PR | NCCHTA 1 | 42 | Full | 4.1 | 64<br>L4 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>these studies were all conducted in similar origin. Could the authors reflect this dependence within studies within the text. | Thank you for your comment with which we agree. Appropriate changes have been made. |
| PR | NCCHTA 1 | 43 | Full | 4.1 | 64<br>L25 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>why children less than 6mths. Age is confounded with size (or more reasonably birth weight as there is a considerable body of evidence to support this). No reasonable evidence was presented to suggest this cut-off. I suggest this is re-worded to reflect that the children are smaller, lighter and frailer. | Thank you for your comment. There was specific evidence indicating the importance of young age as a risk factor. |

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| PR | NCCHTA 1 | 44 | Full | 4.1 | 65<br>L35-L36 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br>It would be beneficial to the audience to present a forest plot of this. Although the results are not significant, it certainly has scientific credibility which should be stated. Please re-word the term "statistical insignificance." | The results of all the diagnostic tests have been tabulated in Table 4.1. Generating forest plots for a large number of outcomes with statistically insignificant results would not be helpful.<br><br>The term 'statistical insignificance' has been reworded |
| PR | NCCHTA 1 | 45 | Full | 4.1 | 65<br>L37-L43 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br>These sentences are poorly written and confused. It is not appropriate to state non-statistical significance here and throughout this document (there are countless examples!). The authors should be reminded they are presenting the evidence and a lack of it does not mean there is no difference, merely that evidence has failed to be exhibited from the sample taken. Please focus on the reliable and presentable evidence. | Thank you. The sentences have been revised. |
| PR | NCCHTA 1 | 46 | Full | 4.2 | 72-75 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Pages 72 to 75, can the authors either provide 95% confidence intervals (or an alternative measure of spread to represent the spread within the data) rather than merely point estimates. This is particularly important when | The study dealing with correlations on page 74 does not provide adequate information about correlation data and this has been highlighted in the text.<br><br>The other studies described on these pages are predominantly cross-sectional surveys/case series which give data on the prevalence of various |

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| | | | | | | dealing with correlations as on page 74, lines 51 to 53 the authors state "an increased correlation". However, if both tests alternative hypothesis were comparing an inclined gradient to a zero gradient independently in both cases this 'may' not be actually true. If 95% CIs are presented the readership would be able to see the variability with both estimates. If the evidence does not provide confidence intervals, standard errors/deviations or ranges it is the authors responsibility to highlight this an a potential limitation to the evidence. | biochemical abnormalities. The study on page 72 (under hypernatraemic dehydration) has compared two proportions and describing the results with p-value is a perfectly legitimate way of giving the results. |
| PR | NCCHTA 1 | 47 | Full | 4.2 | 75<br>L10 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.I**<br>am unfamiliar with the terminology 3.3+17 ? and on line 11 2.4+2.6? particularly since the author states a different between the two ($p<0.05$), but 3.3+1.7 = 2.4+2.6 ? please explain the workings and include 95% confidence intervals to help the audience. | Thank you. This typographical error has been corrected. The values given are of mean ± SD. |
| PR | NCCHTA 1 | 48 | Full | 4.2 | 75<br>L12<br>L15 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>This point is difficult can you revisit this in an alternative manner, maybe by means of a small table ? and compare each individually | Thank you. The results have been tabulated in Table 4.7. Please see the relevant table for further clarification. |
| PR | NCCHTA 1 | 49 | Full | 5.2 | 82<br>L36 | when you quote "there was heterogeneity" state the metric used within the studies to present heterogeneity and what was done about it (i.e. I2, or Q-statistic and p-value, see Cochrane | Thank you for your comment with which we agree. Appropriate changes have been made. |

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| | | | | | | handbook). If nothing was done, highlight it as a limitation within the study and suggest what might be done in future studies.<br><br>Question NCCHTA 1<br>Q3 Full 2.2<br>Please comment on the health economics and/or statistical issues depending on your area of expertise. | |
| PR | NCCHTA 1 | 50 | Full | 5.2 | 82<br>L39 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Please define RD | Thank you. This has been added in the glossary. |
| PR | NCCHTA 1 | 51 | Full | 5.2 | 82<br>L40 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>please define WMD | Thank you. This has been added in the glossary. |
| PR | NCCHTA 1 | 52 | Full | 5.2 | 84<br>L4 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Can the authors confirm the number of observations used to generate this interval, 0.1 to 72 is a huge interval and suggests that very few cases were used, rather than approx 240 in each group. | Thank you. This has been rechecked – the results stand. Kindly see the section on 'studies with zero cell count' in the Cochrane handbook for further clarification. |

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| | | | | | | | |
| PR | NCCHTA 1 | 53 | Full | 5.2 | 84<br>L12 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>This does not make sense. | Thank you this sentence has been revised. |
| PR | NCCHTA 1 | 54 | Full | 5.3 | 87 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Define SMD in the text and the glossary and compare this against the WMD. | Thank you. This has been added to the glossary. |
| PR | NCCHTA 1 | 55 | Full | 6.2 | 104<br>L46 | Why has the author described an ANOVA, then stated a p-value that is clearly a post-hoc t-test. I advise the author to seek the advice of a statistician. | Thank you. This was an error and has been corrected in the text. |
| PR | NCCHTA 1 | 56 | Full | 6.2 | 105<br>L44 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Define what +1.2% +1.1, verses -0.01% + 0.9 ? | Thank you. These are the mean ± SD values. The typographical error has been corrected. |
| PR | NCCHTA 1 | 57 | Full | 6.2 | 106<br>L29 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise. | Thank you. These are the mean ± SD values. The typographical error has been corrected. |

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| | | | | | | Please define what "310+130 verses 172+67" means? | |
| PR | NCCHTA 1 | 58 | Full | 6.2 | 106<br>L30 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Could the authors review their quality status of this study. | Thank you. The study has been re-reviewed and we stand by the evidence level. Methodologically this double-blind RCT had ensured adequate randomization and concealment of allocation. |
| PR | NCCHTA 1 | 59 | Full | 6.2 | 107<br>L11 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Please define "-0.02 + 0.25kg verses -0.14 +0.21 kg" | Thank you. These are the mean ± SD values. The typographical error has been corrected. |
| PR | NCCHTA 1 | 60 | Full | 6.2 | 107<br>L13 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>How do the authors know that the study randomized children, given the title of the study. | Thank you. Despite the title saying it is a 'controlled trial', the study authors had randomly assigned the children to the two feeding groups. This has been rechecked. |
| PR | NCCHTA 1 | 61 | Full | 6.2 | 108<br>L3 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area | Thank you. We could not find these sentences on page 108 as mentioned |

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| | | | | | | of expertise.<br><br>Please reword throughout from "the difference was statistically not significant"… to in this case "there was not enough evidence found to suggest this was a genuine effect (p=XXX), However, it should be reminded these studies were unlikely to be sufficiently powered to detect such a difference". | by the stakeholder. |
| PR | NCCHTA 1 | 62 | Full | 6.2 | 108 L27-L41 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Line 27 to 41. I am uneasy about the inclusion and over enthuses of ref 128 given all the sample size and all the children were male. Please reduce the importance of this study. | Thank you. The study is given an evidence level of EL 1- and has not influenced the recommendations in any way. |
| PR | NCCHTA 1 | 63 | Full | 6.2 | 108 L39 to 41 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>The authors of Ref 128 have compared p-values, please do not repeat their mistake here. A p-value is a simple point estimate and does not describe the variability of the effect size. Therefore it is unfounded and highly unappropriate to suggest that a slightly lower p- | Thank you for your comment. The text has been revised to clarify the comparisons made between the two feeding groups. |

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| | | | | | | value is indicative of a greater treatment effect – This is a mis-interpretation in the original analysis. | |
| PR | NCCHTA 1 | 64 | Full | 6.2 | 109<br>L20 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Provide CI please. | Thank you. The mean (SD) energy intake of the two groups has now been added along with the p-value. |
| PR | NCCHTA 1 | 65 | Full | 6.2 | 110<br>L17 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Please describe evidence collated were from small, low powered studies. | Thank you. Appropriate changes have been made. |
| PR | NCCHTA 1 | 66 | Full | 7.1 | 114<br>L12 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Did you look for studies that compared antibiotic vs antibiotic. Given the ethical considerations this is routinely the case for RCTs. | Thank you for your comment<br><br>We believed it was crucial to determine whether antibiotic therapy was efficacious. Comparison between antibiotics was unlikely to provide convincing information in this regard. For example, an antibiotic (eg amoxicillin) might actually worsen symptoms such as diarrhoea and so a comparison would be unreliable. |

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| PR | NCCHTA 1 | 67 | Full | 7.2 | 115<br>L16 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Line 16, refs 141:143, all have extremely low sample sizes (~15 children per arm) and the author should re-consider the use of these studies individually as well as their quality status [EL 1+] | Thank you for your comment with which we agree. These studies have been included as the 'best available evidence' but their poor quality is now reflected in a downgraded and amended [EL 1-] status. |
| PR | NCCHTA 1 | 68 | Full | 7.2 | 115<br>L26 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Please see above regarding power of refs 141 and 143. | Thank you. This study limitation has been highlighted in the text and evidence summary. |
| PR | NCCHTA 1 | 69 | Full | 7.2 | 115<br>L30 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Line 30. please re-phrase from "diarrhoea improved", as does this mean that the diarrhoea increased in frequency and stool liquidity or decreased. | Thank you for your comment.<br>A definition of the term "improved" has been added (defined as improved stool consistency and decrease in number of stools). |
| PR | NCCHTA 1 | 70 | Full | 7.2 | 116<br>L9 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Please round p-values to 3-sig figs i.e. (p=0.03) | Thank you for your comment. This has been amended as suggested. |
| PR | NCCHTA 1 | 71 | Full | 7.2 | 116<br>L10 | Q3<br>Please comment on the health economics | Thank you for your comment. This is |

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| | | | | | | and/or statistical issues depending on your area of expertise.<br><br>I am confused over the positioning of (p=0.113). The text states a significant finding, but the p-value > 0.1! please justify. | an error and has been amended to p = 0.01. |
| PR | NCCHTA 1 | 72 | Full | 7.3 | 117<br>L13 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>I find it inappropriate to present evidence from ref 145, one arm has only 8 children. Which on lines 17 to 25 breaks down the 8 children to two groups of 4. Could the lead author review their inclusion strategy. | Thank you. Kindly see response to your above comment number 2. |
| PR | NCCHTA 1 | 73 | Full | 7.3 | 118<br>L1 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>I suggest the author re-visits the interpretation of 95% CI 0.98 to 3.51. Since this may be described as providing limiting evidence from erythromycin. | Thank you. The evidence for this observation is again drawn from a small number of patients (n=24). This is discussed in both the Evidence summary and the GDG interpretation satisfactorily. |
| PR | NCCHTA 1 | 74 | Full | 7.3 | 118<br>L15 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Line 15. Please re-word from "too underpowered". As above you can present limited evidence to show an effect. | Thank you. The wording has been amended. |

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| PR | NCCHTA 1 | 75 | Full | 7.8 | 121 L33-L37 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>The level of detail here is not required. Please round these bounds and state exactly what they represent. | Thank you for your comment. This text has been removed for consistency in reporting of non significant findings throughout the guideline. |
| PR | NCCHTA 1 | 76 | Full | 7.5 | 119 L19-L20 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise<br><br>Please use a consistent case for "p-values" | Thank you for your comment. This has been amended.<br>. |
| PR | NCCHTA 1 | 77 | Full | 8 | 128 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Please use forest plots if possible. | Thank you for your comment.<br><br>The chapter has been restructured for greater clarity. Forest plots have been used for most meta-analyses performed in the review. |
| PR | NCCHTA 1 | 78 | Full | 8.2 | 134 L31 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Inconsistent text to quality study rating & [1+] ? please justify | Thank you. This was an error within the evidence summary and has been amended to [EL=1-]. |
| PR | NCCHTA 1 | 79 | Full | 8.2 | 135 L30 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise. | Thank you for your comment. The text has been amended accordingly. |

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| | | | | | | Please expand this and explain the consequence of this finding. | |
| PR | NCCHTA 1 | 80 | Full | 8.2 | 136<br>L27 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Can the author present the ITT population as well as the PPP. I am unsure how confident I am with evidence that has been subjectively captured from a graph? Please expand. | Thank you for your comment.<br><br>The ITT population data have been added as requested. Quantitative data on stool output (in g/hr) were estimated from simple bar charts. The authors give estimates of treatment differences in the text which are drawn from the same data informing the bar charts. |
| PR | NCCHTA 1 | 81 | Full | 8.2 | 138<br>L6 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Please provide a definition of a 'formed stool'. | Thank you for your comment. The study authors have not given any definition of formed stool. |
| PR | NCCHTA 1 | 82 | Full | 8.3 | 144<br>L41 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>The forest plot indicates obvious dependence between the studies included ie. Brooks (20mg) Brooks(5mg) and Fisher Walker x3. Please revisit and determine the dependence/independence of the study populations. It is curious the similarity of the two Brooks studies. | Thank you for your comment. The Brooks outcomes come from a three armed study performed in Bangladesh (20mg zinc vs 5 mg zinc vs placebo) in which the mean duration of diarrhoea for all three treatment arms was found to be 5 days (120 hours). The Fisher Walker study (conducted in three countries) identified an overall non-significant increase in diarrhoea duration in infants receiving zinc. This was in conflict with the Brooks study (which found an overall non significant |

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| | | | | | | | beneficial effect of zinc). The difference in effect may be due to the younger children in the Fisher Walker study (mean 3.2 m vs Brookes 4.0 m) receiving sufficient zinc from breastfeeding (29.8% vs Brooks 6.9% exclusive breastfeeding) to not experience a beneficial treatment effect. |
| PR | NCCHTA 1 | 83 | Full | 8.3 | 146<br>L1 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Same comment as above regarding the independence of the Fisher studies IND/PAK. Particularly given they are the only studies favouring placebo. Please reference the figure. | Thank you for your comment. The Fisher Walker study (conducted in three countries) identified an overall non-significant increase in diarrhoea duration in infants receiving zinc. This was in conflict with the Brooks study (which found an overall nonsignificant beneficial effect of zinc). The difference in effect may be due to the younger children in the Fisher Walker study (mean 3.2 m vs Brookes 4.0 m) receiving sufficient zinc from breastfeeding (29.8% vs Brooks 6.9% exclusive breastfeeding) to not experience a beneficial treatment effect.<br><br>The authors do not give any explanation as to why the results for the IND/PAK study settings differ from the ETH setting. They did state that enrolment in Ethiopia was reduced because of low diarrhoea levels which would perhaps suggest a different |

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| | | | | | | | population and diarrhoeal disease prevalence and aetiology.<br><br>The figure has been referenced in the text. |
| PR | NCCHTA 1 | 84 | Full | 8.3 | 147 L1 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Please describe/reference the figure in the text. | Thank you for your comment. The figure has been referenced in the text. |
| PR | NCCHTA 1 | 85 | Full | 8.3 | 146-148 figures 5,6,7 | Q3<br>Please comment on the health economics and/or statistical issues depending on your area of expertise.<br><br>Please state the limitations and response to the strong degree of heterogeneity found in these tables. | Thank you for your comment.<br><br>There was significant heterogeneity among the studies included in each meta-analysis, although stratification by age group (under 6m, over 6m,) reduced this. The authors of the complete review also adjusted for nutritional status, geographical region, background zinc deficiency, type of zinc given and study setting, but none of these altered the significance of the result. Each subgroup presented heterogeneity, therefore no one single variable explained the heterogeneity found alone. Therefore it might reflect differences in the geographical settings and populations, in definitions of outcome measures, or reporting bias.<br><br>An explanatory sentence has been added to the Evidence summary. |

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| PR | NCCHTA 1 | 86 | Full | Appendix A | 171 L6-L8 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>How does the review (ref 201) break down to children under 5? | Only one study (N=34) included children up to 17 years of age, although one other study (N=100) did not specify the age range. All other studies restricted their population to children under 5. |
| PR | NCCHTA 1 | 87 | Full | Appendix A | 180 Fig 4&5 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Is this figure suggesting that the net cost for a patient this a 10% chance of phlebitis is the same as a patient with a 1% chance ? would this also be the same for a patient with a 75% chance ? | The stakeholder's interpretation is essentially correct, although there is actually a very small increase in the net costs of IVT with an increasing probability of phlebitis (i.e. the line is not quite horizontal). The net costs of IVT would increase by £8 if the probability of phlebitis increased from 0 to 75%. |
| PR | NCCHTA 1 | 88 | Full | 3.1 | 47 13-15 | Q4<br>**How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?**<br>Too much weight was been placed on the RCTs and not enough on the following: The year the data was collected, the country the data comes from and most importantly the sample size. To this page 47, lines 13-15 should be removed. It should also be noted that the data is sparse and have not been collected in large enough number for us to reflect with the UK primary care setting. | Thank you for your comment. Further information (country, sample size) has been now added under the evidence overview.<br><br>However we disagree that lines 13-15 should be removed. It is an accurate summary of the evidence presented. |

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| PR | NCCHTA 1 | 89 | Full | 3.1 | 49 L35-L37 | Q4<br><br>**How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Lines 35-37. This statement is extremely valid, but in its current state its presented in a speculative manner and is not justified. | Thank you. This was included here in error and has been removed. |
| PR | NCCHTA 1 | 90 | Full | 4.1 | 63 L50-L54 | Q4 Full 3.1<br>**How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** From the results quoted, it does not appear that the convergence algorithm has been optimized or the results of ref 72 are reliable. At a guess I would speculate that the authors of ref 72 carried out many hypothesis tests and presented all those they found significant, without regard for the consequence. For example, quoting a 95% CI of an OR from 2 to 797 should be interpreted with considerable caution (line 54). | Thank you. The evidence text has been revised. |
| PR | NCCHTA 1 | 91 | Full | 4.1 | 63 L36- | Q4 Full 3.1<br>**How far are the recommendations based on** | Thank you. We agree with the first part of the comment and appropriate |

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| | | | | | L37 | **the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Please remove the gravity of your statement (6/7 times is not appropriate without justification if this an estimate, then provide variability). It is not reasonable to highlight cows milk and formula in this way. The massive CI bound for both these factor levels instructs the reader that this study only included few babies on these feeding methods. | changes have been made.<br><br>The results have to be documented as they are given in a study. Moreover the GDG were aware of the wide CI's and this did not influence their recommendations. |
| PR | NCCHTA 1 | 92 | Full | 5.3 | 90<br>L2 | Q4 Full 3.1<br>**How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?** Can we be as generic as this ? has the evidence suggested, or exhibited power to present this? I suggest the evidence exhibits a reduction in the need for IV fluids, but can this be as generic as the authors suggest given the evidence? | We were unclear how the question posed related to the recommendation to use low osmolality ORS in line 2 The evidence was taken from well conducted systematic review of 14 trials. Meta-analysis revealed statistically significant results for the outcomes – need for additional IVT (8 trials, n=1996), stool output (11 trials, n=1776) and vomiting (6 trials). Moreover the results were statistically homogeneous. It would have been helpful to receive a positive suggestion on how this evidence can be considered generic! |
| PR | NCCHTA 1 | 93 | Full | 7.4 | 118<br>L31 | Q4<br><br>How far are the recommendations based on the | Thank you. The study authors did not give the exact breakdown of the |

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| | | | | | | findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?<br><br>Can the author offer a breakdown of the children under 16's age variability? i.e. approx how many were < 5 years old. | participants by age. The mean and SD values for age have now been provided. |
| PR | NCCHTA 1 | 94 | Full | 7.10 | 127 L26 | Q4<br>How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?<br><br>I am unconvinced the authors have presented enough evidence to justify these findings. | Thank you for your comment. We agree with you regarding the limitations (the settings and period of publication) of these studies. The GDG did not solely rely on this evidence, and used their clinical experience and expert advice in making a recommendation to avoid the routine use of antibiotics. This is now better clarified in the translation. |
| PR | NCCHTA 1 | 95 | Full | 4<br><br>7 | Throughout Chapter 4, Chapter 7 | **Are any important limitations of the evidence clearly described and discussed?**<br>Throughout the draft, there has been little regard for location of the research. For example, It is known that incidence rates of infection are related with tempreture. In no case the authors have considered potential confounders and discussed effects clustered within country. It should be noted when collating infectious data throughout the world the authors should also consider their relevance to UK primary care. | Thank you for your comment although we do not think this is a correct interpretation. The settings/country of research has been consistently documented under evidence overview. Moreover the applicability of evidence to the UK setting has been highlighted under 'GDG translation from evidence to recommendations' wherever it was deemed to be important, e.g risk factors for dehydration (section 4.1). If there were concerns about the relevance of data to the UK settings |

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| | | | | | | | (incidence of causative pathogens in stool (section 3.2.1) or incidence of biochemical abnormalities (section 4.2)), the evidence was taken predominantly from UK based studies. |
| PR | NCCHTA 1 | 96 | Full | 7 | | Q<br>Are any important limitations of the evidence clearly described and discussed?<br>The majority of studies presented within this chapter were conducted within a period of liberal antibiotic prescription. Throughout the UK we are experiencing increased treatment failure because of raised antibiotic resistance. Could the authors be reminded of a need to reflect this limitation due to the worldwide change in policy toward antibiotics. | Thank you for your comment. We agree with you regarding limitations (the settings and period of publication) of these studies. We have not placed any reliance on them in making a recommendation to avoid the routine use of antibiotics. This is now better clarified in the translation. |
| PR | NCCHTA 1 | 97 | Full | 8.2 | 138 L31-L32 | Are any important limitations of the evidence clearly described and discussed?<br><br>Are the population boys or children ? if the study uses only boys, what bias'es are introduced from this selection bias ? | The population are boys and not children. This has been amended in the text. The main difference in recruiting only boys rather than girls and boys to a study is that a more accurate estimation of stool output is possible as urinary output is more readily separated.<br><br>Studies including children may tend to overestimate stool output compared to 'boys only' studies, rendering comparison across studies inappropriate in 'quantitative' data analysis. This is not an issue here. |

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| PR | NCCHTA 1 | 98 | Full | General | | Q5<br>Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.<br><br>I would encourage the use of Forest plots throughout the earlier part of this document. | Thank you for your comment. Forest plots have generally been used where meta-analyses have been presented (mostly in other therapies chapter). We could not discern from where you felt they were missing in the earlier part of the document. |
| PR | NCCHTA 1 | 99 | Full | General | | Q5<br>Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.<br><br>I would encourage the consistent use of CI throughout this report. I have highlighted some, but not all of the occaisions where CIs would allow the readership an opportunity to gain a greater understanding of the evidence as well as being able to decipher some of the more curious results/conclusions. | Thank you. The team has followed a uniform policy of documenting the 'confidence intervals' if the results were statistically significant or important from a clinical perspective. Reporting CI's for all the results (even if insignificant) might discourage most readers from reading this guideline. However the detailed statistical information is given in the evidence tables, and can be referred by a reader curious wanting more on it. |
| PR | NCCHTA 1 | 100 | Full | General | | Q5 Full 4.1<br>Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have | Thank you. The primary publication of the full document is in printed hard copy and its representation on the web reflects this. We are unable at this time |

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| | | | | | | been reached from the evidence.<br><br>It would help if there was a direct link from the reference in the report to the table of studies, without having to look up the study number in the back of the report. | to primarily publish a web version of the full guideline. |
| PR | NCCHTA 1 | 101 | Full | General (Glossary) | | Q5<br>**Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**<br><br>The authors have not cross references the terms within the glossary to ensure they are included within the guidance document, for example: Absolute Risk, Absolute Risk Reduction, Acutephase Proteins, Acute Sector, Applicability, Diagnostic Study, Experimental Event Rate, etc, etc. | |
| PR | NCCHTA 1 | 102 | Full | Glossary | | Q5 Full 4.1<br>**Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**<br>I have highlighted many examples in the glossary where the author is unsure about certain statistical definitions. Please review and ensure all terms are succinct and scientific. | Thank you for your comments on the glossary. It has now been revised with updated scientific definitions. |

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| PR | NCCHTA 1 | 103 | Full | 2.5 | 44 | Q5<br>Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.<br>The figure has the potential to be really useful. However, it is currently unclear and has a combination of attempting to be both too inclusive, but lacks information. For example, where is Table 4.6 (a page number of link would be very useful). I would suggest that the flow diagram is simplified, but a number of smaller tables follow offering the more detailed information. | Thank you for your comment. A revised flow pathway has been presented. |
| PR | NCCHTA 1 | 104 | Full | 7.3 | 117<br>L41 | Q5<br>Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.<br><br>Please define "3.2 +/- 1.7 days". The readership is unlikely to know what this terminology means throughout this report. | Thank you for your comment. The formatting for mean values and standard deviations has been amended throughout the guideline. This particular example has been removed for consistency in reporting of non significant findings throughout the guideline. |
| PR | NCCHTA 1 | 105 | Full | 8.3 | 144<br>L41 | Q5<br>Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have | Thank you for your comment. This has been amended. |

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| | | | | | | been reached from the evidence.<br><br>Please improve the presentational quality of the figure. | |
| PR | NCCHTA 1 | 106 | Full | 8.3 | 145<br>L7 | Q5<br>Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.<br><br>A forest plot is an exceptional way to describe these data but the figure is poorly described in the text. | Thank you for your comment. The forest plot has been correctly inserted to complement the text given. |
| PR | NCCHTA 1 | 107 | Full | 8.3 | 145<br>L7 | Q5<br>Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.<br><br>Where is figure 4 ? | Thank you for your comment. The forest plot has been correctly inserted to complement the text given. |
| PR | NCCHTA 1 | 108 | Full | 8.4 | 155 | Q5<br>Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence<br><br>Please reference figures 8 and 9 in the text. | .<br>Thank you for your comment. The figures have been referenced in the text. |
| PR | NCCHTA 1 | 109 | Full | 8.4 | 155<br>L8L5 | Q5<br>Is the whole report readable and well | Thank you for your comment. |

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| | | | | | & | presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.<br><br>The author states "There was heterogeneity…", can they offer a better explanation of what was then carried out ? The Cochrane Handbook suggests this should trigger a number of things. In Figure 8, the implications of heterogeneity could have an impact on the overall conclusion. This is less likely to be the base in Figure 9. However, in both cases I suggest the authors report what the original authors did and outline current standard practice they ignored this, explain what they would suggest the authors highlight this as a limitation | Additional explanation discussing the identified heterogeneity has been added to the evidence summary of this section. |
| PR | NCCHTA 1 | 110 | Full | 3.1 | 50<br>L2 | Q6<br>Please comment on whether the research recommendations, if included, are clear and justified.<br><br>This introduces a min sample size & is inconsistent with the rest of the report. | See comment NCCHTA1 33.<br><br>There were no comparative studies to inform this question on characteristics (signs & symptoms) of alternative diagnosis, and the best available studies were case series. Being an evidence-based guideline, it was decided to include these studies but improve the quality by pragmatically introducing a minimum sample size. The evidence was further supplemented by the NICE published guideline on 'Feverish illness in children' and the knowledge/ experience of the GDG members. This has been now made clearer in the text. |

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| | | | | | | | We disagree regarding consistency of approach. The methodology followed in this guideline is robust and based on the NICE guidelines standard – see manual. It aims to look at the best available evidence.<br>. |
| PR | NCCHTA 1 | 111 | Full | 3.1 | 51<br>L12-L13 | Q6<br>**Please comment on whether the research recommendations, if included, are clear and justified.**<br>where has the cut off of both 3 months and 380-390 been argued and justified? | Thank you. The GDG recognised that high fever is uncommon in children with gastroenteritis. The specific levels chosen as cut-offs were empirically chosen, merely as a guide to healthcare professionals. The lower temperature in young infants was consistent with the advice in the NICE published guideline on 'Feverish illness in children'. Kindly see the link below for more details<br><br>http://www.nice.org.uk/Guidance/CG47/Guidance/pdf/English |
| PR | NCCHTA 1 | 112 | Full | 4 | 64 | Q6<br>**Please comment on whether the research recommendations, if included, are clear and justified.**<br>Would it be possible to speculate using UK expert opinion what influences are different in the UK. The evidence collated is dominated from the sub-continent. | Thank you. The applicability of all the risk factors in the UK setting has been adequately described under 'GDG translation from evidence to recommendations'. Kindly see the relevant section for more details. |
| PR | NCCHTA 1 | 113 | Full | General | | Q6 | |

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| | | | | | | **Please comment on whether the research recommendations, if included, are clear and justified.**<br>It is clear this guideline appears to have been put together by separate groups by experts with differing views which studies should be included and excluded. It would be helpful if a consistent approach to the following was carried out or amended within the individual subsections:<br>Search strategies e.g: which journals (Medline, Pubmed, Web of Science, etc) and which terms were used e.g. (Diarrhoea AND vomitting AND etc, etc).<br>Quality checklist was used ? ( )<br>Study types (RCT, CBA, ITS, etc). | Thank you. A search appendix has been provided which should provide clarification |
| PR | NCCHTA 1 | 114 | Full | General | | Q6<br>**Please comment on whether the research recommendations, if included, are clear and justified.**<br>When dealing with study types the following should be considered:<br>attrition rate, sample size, randomization, blinding and other quality checklists authors could present a simple table of biases at the start of each section (see Cochrane Collaboration Handbook, Feb 2008) | Thank you. This is a NICE guideline. Kindly note that there is a well defined methodology given in the NICE technical manual. See the link for more details.<br>http://www.nice.org.uk/page.aspx?o=guidelinesmanual |
| PR | NCCHTA 2 | Q1 | Full | 1.1 | | Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached) | No response required |

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| PR | NCCHTA 2 | Q2 | Full | 2.1 | | Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelines manual). | No response required |
| PR | NCCHTA 2 | Q3 | Full | 2.2 | | Please comment on the health economics and/or statistical issues depending on your area of expertise. | No response required |
| PR | NCCHTA 2 | Q4 | Full | 3.1 | | How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected? | No response required |
| PR | NCCHTA 2 | Q5 | Full | 3.2 | | Are any important limitations of the evidence clearly described and discussed? | No response required |
| PR | NCCHTA 2 | Q6 | Full | 4.1 | | Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence. | No response required |
| PR | NCCHTA 2 | Q7 | Full | 4.2 | | Please comment on whether the research recommendations, if included, are clear and justified. | No response required |
| PR | NCCHTA 2 | Q8 | Full | 5. | | additional comments | No response required |
| PR | NCCHTA 2 | 1 | Full | | | No comments | Thank you |
| PR | NCCHTA 2 | 2 | Full | | | See below (ie NCCHTA 2 comments Q3-8) | No response required |
| PR | NCCHTA 2 | 3 | Full | Appendix A | 169 | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>In the 'cost-effectiveness analysis' of IVT vs ORT, the authors do not undertake a cost-effectiveness analysis they instead conduct a cost-minimisation analysis. This approach has | Thank you for this comment although we don't agree with the criticism implied. Some of the comments raised here by the stakeholder are also considered in the Discussion in Appendix A.<br>On a semantic point, cost-minimisation is not an alternative method of |

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| | | | | | | largely been discredited in the general economic evaluation literature because it can rarely been assumed that the alternatives under evaluation yield exactly the same outcome. As a minimum the authors should give the evaluation its correct name- cost-minimisation NOT cost-effectiveness analysis | economic evaluation to cost-effectiveness but a sub-set or special case of it. Therefore, it would not be wrong or incorrect to label a cost-minimisation analysis as cost-effectiveness even if we accepted that that is what this analysis amounted to. Our reasons for preferring the cost-effectiveness label are listed below:<br>i) Experience on GDGs suggests that the perception that health economics is about minimising costs is commonplace. On these grounds alone we prefer the cost-effectiveness label but in doing so we also make clear the assumption about equivalent effectiveness so that the importance of effectiveness in determining efficient decisions in health care is hopefully not lost<br>ii) We relax the assumption about equivalent effectiveness as part of a threshold analysis and therefore the analysis truly is not restricted to a simple comparison of costs.<br>Nor do we accept that a cost-minimisation 'approach' has been discredited, as that implies something suspect with the method. However, we accept that many health economists would rarely consider it the most appropriate technique as it is unusual that the 'alternatives yield exactly the same outcome'. Of course, statistically it is very unlikely that alternatives |

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| | | | | | | | compared in a clinical trial or meta-analysis would give identical effect sizes even if there was no treatment benefit of one alternative over another. As a general case we would argue that cost minimisation may indeed sometimes be a reasonable simplifying assumption, especially in a context of informing evidence based guidelines, when there really is a lack of good evidence of any treatment effect and/or that the observed differences are not clinically important.<br>In this particular case we are comparing two treatments that both achieve "cure". The "different outcome" that may exist relates to time to cure, measured in hours. Yet we know that the maximum QALY that can be gained from a 24 hour difference in time to cure is 0.0027 QALYs (apart from where there health states worse than death). Here we are taking a small fraction of 24 hours and disease states that are almost certainly judged considerably better than death. At some point some sensible rounding of very small QALY gains is surely reasonable? We believe that any small temporal gain in QALY in this case is so small that it can reasonably be ignored. Nevertheless, we are aware of the potential criticism of such an assumption and undertake a threshold analysis to assess the QALY gain that |

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| | | | | | | | would be needed for cost-effectiveness given the cost differences between the alternatives. Unsurprisingly this showed that a much bigger QALY gain than could ever be expected from a small improvement in time to cure would be needed for the more expensive treatment option to be considered cost-effective. |
| PR | NCCHTA 2 | 4 | Full | Appendix A | 169- | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>I am unconvinced by the argument that because all cases end up getting rehydrated anyway then there are no outcome differences. Surely, if some cases under OPT get rehydrated later then their quality of life is relatively worse for the intervening hours, and this should be taken account of explicitly in the main analysis rather than as a threshold analysis. I would therefore prefer to see the HrQOL decrement even if only small, and imperfectly estimated, included directly in the comparison | Response also contained in above – the small HRQOL decrement being alluded to "for the intervening hours" would most likely to be less than 0.0005 QALY (with a concomitant WTP of <£10). All modelling involves a simplification of the real world, and sometimes a simplifying assumption of equivalent effectiveness may be defensible. |
| PR | NCCHTA 2 | 5 | Full | Appendix A | 169- | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>At various places the authors use statistical significance as a justification for excluding events of interest, a much more conventional approach would be to keep the events of | We presume that this comment is made with particular reference to Table 1 in appendix A. We accept the general premises behind this comment but believe our exclusion of non-significant complications was justified in this case. Of the five excluded non-significant complications reported in the meta- |

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| | | | | | | interest in the analysis, and allow the mean differences and the uncertainty around it to be propogated through the model. This avoids potentially important events being excluded that the primary studies were not powered to detect | analysis, three of them had no difference in means. Of course there is uncertainty around this zero mean difference but it is difficult to see how including this in the model would aid a guideline recommendation for one alternative over another.<br>For hyponatremia there is a difference in means but the data using a random effects model is highly consistent with a null hypothesis of no difference (p=0.9; 95% CI [-0.13 to 0.15]. It should be remembered that economic models are intended to support recommendations in the here and now. The data from a meta-analysis of 1,800 children) was consistent with no difference in hyponatremic complications. The meta-analysis may not have been powered to detect a difference but given the sample size of the meta analysis this suggests that any 'real' difference that may exist is likely to be very small. Furthermore, it is most improbable that research would ever be undertaken which would be powered to detect such a small difference. Whilst hyponatremia is an important complication, guideline economists do not generally have the time to do an expected value of perfect information analysis to determine whether such research may actually be worthwhile.<br>Finally, abdominal distension was more borderline in terms of statistical |

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| | | | | | | | significance. However, the clinical view, without unpicking the component reviews of the meta-analysis, was that most of the cases of abdominal distension with ORT would have no clinical significance.<br>We will add something to the text to justify our exclusion of non-significant complications in more detail. |
| PR | NCCHTA 2 | 6 | Full | Appendix A | 173 | Q3 Full 2.2<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>Some aspects of the costing are unclear. In particular the authors state that they have included the costs of capital and facilities on page 173, but then later on the same page state that the ORT costs only include staff and consumables time, i.e. the capital costs (for both alternatives) of being in the ER are excluded. This would only matter if the time in the ER differed by treatment but it is not unclear whether this is the case? | Thank you. We accept the wording is unclear and will amend.<br>ED attendance costs (and times) are the same for both IVT and ORT and therefore capital costs associated with use of ED facilities have been excluded from the analysis. However, staff and consumable costs for both treatment alternatives differ. ORT patients are discharged following treatment and incur no further costs. However, IVT patients do incurs further costs due to an additional inpatient stay. |
| PR | NCCHTA 2 | 7 | Full | Appendix A | 176 | Q3 Full 2.2<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>How many hospital days does the cost of £602 relate to in Table 7, later in Table 10 it suggests this is for 1 day which seems 'high' ? | The National average cost for HRG code PA21 for the HRG label 'Infectious & Non Infectious Gastro without complications' is £602. The average length of stay given by reference costs is one day. |
| PR | NCCHTA 2 | 8 | Full | Appendix A | 179- | Q3 | The comment regarding the |

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| | | | | | 182 | **Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>In general I found the sensitivity analyses uninformative, the ranges used were not that plausible and the whole thing rests on the assumption of no incremental gain in outcome, an assumption considered somewhat belatedly on page 183. | assumption of no incremental gain has been in addressed in earlier responses to this stakeholder. We think that the sensitivity analysis, including the threshold analysis on page 183, show that the conclusion that ORT is cost-effective is not particularly sensitive to the baseline inputs/assumptions. The ranges were chosen to demonstrate this lack of sensitivity. If they are not plausible, they nevertheless include all the relative values as a subset. |
| PR | NCCHTA 2 | 9 | Full | Appendix B | | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>The same concern applies as for appendix A it seems somewhat brave and unconventional to just assume that there is no difference in outcome between the interventions, in this case it appears that the little evidence available suggests the intervention improves outcome (at least if measured by cessation of vomiting) yet this is disregarded in the 'health economics' which just looks at the relative costs. | Thank you for this comment. However, it is not the case that we assume no difference in outcome between the interventions (one of which is 'do nothing'). The results effectively show a position of dominance with net savings and reduced vomiting. Nevertheless, we are sufficiently concerned by this comment that we will amend the text so this is clear. |
| PR | NCCHTA 2 | 10 | Full | Appendix B | | Q3<br>**Please comment on the health economics and/or statistical issues depending on your area of expertise.**<br>No sensitivity analysis is undertaken. There is absolutely no measure of uncertainty, statistical | This was not undertaken due to the guideline context. The GDG did not recommend ondansetron as in addition to evidence showing a beneficial impact on cessation of vomitting there was also some evidence that it |

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| | | | | | | or methodological. | increased diarrhoea. The GDG were sceptical as to whether this increase in diarrhoea had clinical significance but therefore felt further research was needed before cost-effectiveness could be demonstrated. This is reflected in a research recommendation coming from the guideline. It was therefore felt not critical to explore uncertainty further. Nevertheless, on reflection we think that some sensitivity analysis would be helpful and have added this to the Appendix B analysis. We also have amended the text to give the reader a better idea of the context in which the analysis was undertaken. |
| PR | NCCHTA 2 | 11 | Full | 2 | 34-43 | Q4<br>How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?<br><br>They seem reasonable but note only two of the therapies have been subjected to any health economic evaluation at all | Many of the clinical questions did not relate to recommendations which would involve a decision between competing alternatives (e.g. What factors are associated with an increased risk of dehydration?). The GDG identified a number of questions where there was potential for economic analysis. However, as the evidence was reviewed it became evident that the many recommendations would not result in either a major change in current clinical practice or carry a significant cost impact. Nevertheless, we accept that there needs to be more explanation of the topics chosen and not chosen for economic analysis and |

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| | | | | | | | have added this to the text. |
| PR | NCCHTA 2 | 12 | Full | | | See above | No response required |
| PR | NCCHTA 2 | 13 | Full | all | | Q6<br>**Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**<br>More effort could be made to better integrate the health economics into the main report. | It would have been helpful here to have had some positive suggestion as to how "to better integrate the health economics into the main report". We have tried to improve the integration by a) better explanation of topic selection for health economics b) improving evidence statements/GDG translation where relevant. |
| PR | NCCHTA 2 | 14 | Full | 1.73 | 32 | Q6<br>**Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**<br>In the health economics section the authors do not define the two clinical questions that they apply the health economics to. Also the appendices that they refer to are given as X and Y, then they should actually refer to A and B. | Thank you. The clinical questions incorporating Health Economics is now stated and the appendix labelling corrected. |
| PR | NCCHTA 2 | 15 | Full | Appendix A | 171 | Q6<br>**Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**<br>Its unnecessary and unclear to split the model into 3 figures, could easily be integrated into 1 | On reflection we agree with this comment and have amended as suggested. |

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| | | | | | | figure | |
| PR | NCCHTA 2 | 16 | Full | Appendix A | 172-173 | Q6<br>**Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**<br><br>Table 1 crosses over 2 pages | Thank you. This will be resolved during copy editing. |
| PR | NCCHTA 2 | 17 | Full | Appendix A | Page 173 | Q6<br>**Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**<br>Including the formula for calculating annual equivalent cost is rather unnecessary | Perhaps, although in the interests of transparency we feel it helps the reader (who may be unfamiliar with costing methodology) to understand how the costs are derived. |
| PR | NCCHTA 2 | 18 | Full | Appendix B | 185 | Q6<br>**Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**<br>Table 2, the title is uninformative | Thank you. The title of this table has been amended. |
| SH | Abbott Laboratories | 1 | Full | 8.2.2 | 136 | The evidence overview for antisecretory agents states that there were "*two randomised placebo controlled trials of racecadotril identified*". However, there are three additional published studies in children that should be included in the | Thank you for your comment.<br><br>The Cojocaru 2002 study was published in French and would not be |

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| | | | | | | evidence for racecadotril (two randomised trials and a systematic review with meta-analysis):<br><br>1. Cojocaru B, Bocquet N, Timsit S, et al. Effect of racecadotril in the management of acute diarrhea in infants and children. *Arch Pediatr* 2002; **9**: 774–9.<br><br>2. Turck D, Berard H, Fretault N, Lecomte JM. Comparison of racecadotril and loperamide in children with acute diarrhoea. A*liment Pharmacol Ther* 1999; **13** (Suppl. 6): 27–32.<br><br>3. Szajewska H, Ruszczynski M, Chimielewska A, Wieczorek J. Systematic review: racecadotril in the treatment of acute diarrhea in children. *Aliment Pharmacol Ther* 2007;**26**:807-813.<br><br>Abbott considers that had these additional trials been included in the evidence base, there may have been sufficient evidence to recommend racecadotril as an adjunct to ORS in children under 5 in England and Wales. Currently, the GDG list further studies evaluating the safety and efficacy of racecadotril as a research recommendation, and do not recommend any antidiarrhoeal medications in the draft guidelines.<br><br>Abbott suggests these studies are included in the evidence for racecadotril in the guidelines. If the GDG do not include them, then a reason for their exclusion should be given. | included according to NICE guideline development procedure. The Turck 1999 study was identified from searches and excluded from the review as it compared racecodotril to loperamide (rather than to placebo or no treatment). The systematic review of three trials comparing racecadotril to placebo by Szajewska 2007 was identified in searches. Because insufficient detail was provided within the systematic review it was excluded. However, the two constituent trials published in English (Cezard and Salazar Lindo) were retrieved in full copy and included. The third French paper (Cojocaru 2002) was excluded.<br><br>These exclusions will be specified in the excluded studies tables. |
| SH | Abbott Laboratories | 2 | Full | 8.2.2 | 136 | When discussing the Cezard[I] study in the | |

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| | | | | | | evidence overview (line 27), the GDG state that "*Only per-protocol results were reported here but these were not clearly presented and most outcome measurements were estimated from graphs.*" In this paper, the authors do present results in the text and graphically for both the full data analysis results and the per-protocol analysis. Abbott suggests that the statement is removed from the evidence overview because it is incorrect. | Thank you for your comment.<br><br>The text has been amended to include both the full data and per-protocol analyses presented in the Cezard study, as suggested. |
| SH | Abbott Laboratories | 3 | Full | 8.2.2.1 Racecadotril | 137 | The guidelines state: *"Racecadotril (1.5 mg/kg body weight) (n = 89) or placebo (n = 83) was randomly administered as a powder three times daily for 5 days or until diarrhoea stopped if earlier. Rehydration was administered orally or by gastric tube without restriction. Treatment given for 5 days or until diarrhoea stopped."* The information around treatment duration is mentioned twice here. | Thank you for your comment.<br><br>The text has been amended to remove the duplicated sentence. |
| SH | Abbott Laboratories | 4 | Full | 8.2.2.1 Racecadotril | 137 | *Outcome - hourly stool output in first 24 hours*<br><br>The mean hourly rate of stool production in the first 24 hours has been presented using the 'n' numbers from the per-protocol analysis, but the rest of the data shown i.e. actual rate and percentage difference between racecadotril and placebo are from the full data set. The data should either be the full data set or the per-protocol analysis and not a mixture of the two. Therefore the following sentence should be changed to: "This was found to be lower in the racecadotril group **(*n* = 85)** (11 g/hour) compared to the placebo group **(*n* = 82)** (16 g/hour). " | Thank you. As suggested, the text has been amended to include information from the full data and per-protocol analyses. |
| SH | Abbott Laboratories | 5 | Full | 8.2.2.1 | 138 | In the following sentence (Line 1): "*However, in* | Thank you. This p value has been |

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| | | | | Racecadotril | (Line 1) | *the placebo group the rotavirus positive participants had a median duration of diarrhoea of 72 hours compared to 52 hours in the rotavirus negative participants*" the statistical significance needs to be added: **(P<0.001 for the comparisons between treatments and rotavirus-status groups).** | added. |
| SH | Abbott Laboratories | 6 | Full | 8.2.2.1 Racecadotril | 138 | *Outcome – 'cure rate' at 5 days*<br><br>This outcome measure needs to reference Salazar-Lindo [ref 168], as it is currently unreferenced.<br><br>It might be worth adding **(n=67)** or **66%** to the part of the sentence that refers to placebo, as if it is read out of context it is unclear as to the proportion of placebo patients that are 'cured' at 5 days. Abbott suggests the sentence is amended to: *"In all participants, at 5 days, 57 of the racecadotril group (n = 68; 84%) were cured of diarrhoea (passing of two consecutive formed stools or not having passed a stool for 12 hours) compared to 44 (n = 67; 66%)cured participants in the placebo group."* | Thank you. Appropriate changes have been made in the text. |
| SH | Abbott Laboratories | 7 | Full | 8.2.2.1 Racecadotril<br><br>Evidence summary | | As previously mentioned in comment 1 there are more than two randomised controlled trials evaluating the efficacy and safety of racecadotril. Abbott suggests that the following two RCTs are added to the evidence base for racecadotril. Summaries of the trials have been presented in a review paper by Maldonado[ii]:<br><br>Turk et al[iii]<br>*In a multi-centre, randomised, double-blind study controlled by double placebo, compared* | Thank you for your comment.<br><br>The Turck 1999 study was identified from searches and excluded from the review as it compared racecodotril to loperamide (rather than to placebo or no treatment). The Cojocaru 2002 study was published in French and would not be included according to NICE guideline development |

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| | | | | | | *racecadotril (1.5 mg/kg/8 hrs) with loperamide (0.03 mg/kg) in the treatment of 102 children (2 - 10 yrs). No significant differences were found in faecal output or diarrhoeal duration. However, there were differences in tolerance, with a lower incidence of constipation and fewer associated treatment modifications in the patients receiving racecadotril*.[ii]<br><br>This is an important consideration given that loperamide is not used in the UK in children under 5 due to its side effect profile. Turk showed that racecadotril is as effective as loperamide in controlling diarrhoea but demonstrated a superior tolerability and safety profile.<br><br><u>Cojocuru et al</u>[iv]<br>*Cojocaru et al studied the number of Emergency Room visits, number of depositions, and severity of symptoms during the first 48 hrs in 166 children (3 months – 3 yrs) with acute diarrhoea. The need for a second visit was less frequent (14/76 vs. 27/78), number of depositions was lower (6.8 ± 3.8 vs. 9.5 ± 4.5), total diarrhoeal duration was shorter (97.2 ± 35.6 hours vs. 137.7 ± 42.4 hours), hydration status was better and a lower number of hospitalisations were required in the children treated with racecadotril compared with those who were not*.[ii]<br><br>This open-label, randomised trial demonstrated that significant differences in prominent outcomes were observed in patients given | procedure. The systematic review of three trials comparing racecadotril to placebo by Szajewska 2007 was identified in searches. Because insufficient detail was provided within the systematic review it was excluded. However, the two constituent trials published in English (Cezard and Salazar Lindo) were retrieved in full copy and included. The third French paper (Cojocaru 2002) was excluded. |

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| | | | | | | racecadotril; namely the number of medical visits ($p < 0.05$), the number of stools ($p < 0.001$) and the amount of time the diarrhoea lasted ($p < 0.00000001$) were all reduced in the treatment group. This may have financial implications in the NHS in England and Wales, given that racecadotril-treated patients required fewer hospitalisations. Furthermore, cost-savings arising from a reduction in unscheduled hospitalisation and in repeat consultations will be realised almost immediately given that diarrhoea is an acute condition. This is unlike chronic disease areas, where cost benefits may not be realised until years in the future.<br><br>Finally, Szajewska and colleagues[v] conducted a systematic review of the evidence for racecadotril. The authors reported that "*three randomised-controlled trials (471 participants) met the inclusion criteria. Two trials reported stool output, and data suggested less stool output in the racecadotril group than in the control group. The duration of diarrhoea was significantly reduced in the three trials reporting this outcome. Achievement of a cure by day 5 was similar in both groups. Adverse effects were similar in both groups.*"<br><br>To conclude, the evidence summary for racecadotril in the draft guidelines should be updated to include the two RCTs and the systematic review. | |
| SH | Abbott Laboratories | 8 | Full | 8.2.3 | 143 (Line 3) | **Recommendation on anti-diarrhoeal agents**<br><br>The GDG currently do not recommend any | Thank you for your comment. The GDG was concerned about the |

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| | | | | | | antidiarrhoeal medications in the draft guidelines for the management of acute diarrhoea and nausea due to gastroenteritis in children under five.<br><br>The trials have clearly demonstrated that racecadotril as an adjunct to ORS is an effective treatment option for children under five with acute diarrhoea.<br><br>Abbott suggests therefore, given the additional evidence presented above, that this recommendation is amended so that racecadotril is included as a treatment option for clinicians to consider in the overall management of diarrhoea. | possibility that this agent might exacerbate diarrhoea. On that basis a recommendation for further research was made looking at safety and cost-effectiveness in the UK setting. As the additional evidence presented cannot be included, there is no reason to change the recommendation. |
| SH | Abbott Laboratories | 9 | NICE | 1.6.1 | 20 | In line with comment 8, Abbott suggests that the recommendation in Section 1.6.1 for antidiarrhoeal agents in the NICE version of the guideline is amended so that racecadotril is included as a treatment option for clinicians to consider as part of the holistic management of acute diarrhoea due to gastroenteritis. | Thank you. As explained earlier, the evidence that Abbott has requested for inclusion, is not admissible. Therefore, the recommendation is unchanged, |
| SH | Alder Hey Childrens NHS Foundation Trust | 1 | NICE | 1.1.1.3 | 12 | Photophobia is a very unhelpful sign of meningitis in children, few parents can detect it even if present. Childhood bacterial meningitis: initial symptoms and signs related to age, and reasons for consulting a physician.Valmari P, Peltola H, Ruuskanen O, Korvenranta H. Eur J Pediatr. 1987 Sep;146(5):515-8.<br><br>Shouldn't advice be taken from the NICE meningitis GDG on features suggesting Meningitis and Meningococcal disease?? | Thank you this has been amended. |
| SH | Alder Hey Childrens | 2 | NICE | 1.1.2.1 | 12 | If there is a history of recent overseas travel a | |

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| | NHS Foundation Trust | | | | | stool culture should always be sent, not just considered<br>Children with traveller's diarrhoea have much more bacterial and protozoal infections than other children [Riordan FAI, Quigley T, West N. Travel associated diarrhoea in children admitted to hospital. J Infect 2000;40:A28]<br>Stool culture was the commonest positive investigation in children presenting with fever after travel abroad. [West NS, Riordan FA. Fever in returned travellers. Arch Dis Child 2003;88:432–4] | Thank you. The GDG considered your comment, but decided that stool culture is not necessary for all children.<br><br>The studies referred are non comparative studies and do not provide robust evidence. |
| SH | Alder Hey Childrens NHS Foundation Trust | 3 | NICE | 1.1.2.6 | 13 | *Consider measuring C-reactive protein (CRP) in young infants and in children with immune deficiency presenting with diarrhoea and fever.*<br>This is meaningless. In this situation you should be doing much more (FBC, Blood cultures, urine, and consider antibiotics) – just considering a CRP would miss serious infection | Thank you for highlighting this. The GDG considered this and have removed this recommendation. |
| SH | Alder Hey Childrens NHS Foundation Trust | 4 | NICE | 1.1.2.7 | 13 | *Monitor full blood count, platelets, urea and electrolytes in children with E. coli 0157:H7 infection*<br>How often and for how long? 2-3 times a week for 7-10 days? | Thank you. The recommendation has been revised to monitor for HUS in consultation with a specialist. |
| SH | Alder Hey Childrens NHS Foundation Trust | 5 | NICE | 1.2.2.2 | 16 | Which clinical manifestations are suggestive of hypernatraemia? Please add these | Thank you. Please see the recommendation on hypernatraemic dehydration (rec 1.2.1.4). |
| SH | Alder Hey Childrens NHS Foundation Trust | 6 | NICE | 1.5.2 | 20 | *Give appropriate antibiotic treatment to those with extra-intestinal metastatic bacterial infection*<br>This is an odd phrase – if there were bacterial infection in the body outside the gut, surely everyone would use antibiotics? | We agree with your comment and the recommendation has been reworded. It is presented to reinforce the good clinical practice that you highlight. |

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| SH | Alder Hey Childrens NHS Foundation Trust | 7 | NICE | 1.5.3 | 20 | *Consider antibiotic therapy for those recently returned from overseas travel.*<br>This should depend on culture and sensitivity results of stool sample. | Thank you. In light of your comment, this recommendation has been reworded to<br><br>'Consider antibiotic therapy, following specialist advice, for children who have recently been abroad' |
| SH | Alder Hey Childrens NHS Foundation Trust | 8 | General | | | When (if ever) should C diff toxin be tested for in children? | Thank you for your comment. |
| SH | Alder Hey Childrens NHS Foundation Trust | 9 | NICE | 1.2.1.3 | 14 | Acute changes in child's weight signify fluid loss. Often for babies, parents have 'red book' recent weight records available for comparison with current weight. | Thank you. Although, the GDG recognised that if an accurate and very recent weight record was available prior to the onset of the diarrhoeal illness this might provide a guide to percentage weight loss. The reliability of this approach was not certain however, and the GDG doubted that it was often relied upon. |
| SH | Alder Hey Childrens NHS Foundation Trust | 10 | NICE | 1.3.1.1 | 16 | Preventing dehydration: advice is to continue milk and breast milk, but only implies stopping solids, if oral rehydration fluid given. For how long? Just the 4 hours duration of ORS? Please could you clarify this? | Thank you. This has been clarified now under recommendations under nutritional management (recs 1.4.1.1 and 1.4.1.2). |
| SH | Alder Hey Childrens NHS Foundation Trust | 11 | NICE | 1.3.1.1 | 16 | Given the guide criteria, almost every child I see at RLCH A&E would be given ORS, presently most mothers are advised to give increased water, small and often if the children are not dehydrated. Could you qualify your ORS type and comment on using flavoured varieties. Most babes /children > 9/12 refuse plain dioralyte etc as it tastes salty/foul….wheras infants seem to | Thank you. The types of ORS recommended have now been highlighted in a footnote under the relevant recommendation. |

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| | | | | | | enjoy it | |
| SH | Alder Hey Childrens NHS Foundation Trust | 12 | NICE | general | | Please can you make this as short and user friendly as possible…….A sheet of A4 gets read and re read. Most of the rest gets stuck in the 'pile, to be read one day' then binned 5 yrs later ! | NICE would be developing a 'Quick reference guide (QRG)' version of this guideline which would be similar to what you suggest. |
| SH | Alder Hey Childrens NHS Foundation Trust | 13 | general | General | | Wish you all the best with your endeavour. | Thank you. |
| SH | Alder Hey Childrens NHS Foundation Trust | 14 | general | General | | I have given this document a quick read (which isn't easy) and it does not seem to show any awareness of potential surgical pathologies. I believe that the document should alert clinicians to the possible "missed diagnoses" of **appendicitis, intussusception, volvulus, and incarcerated herniae**, in particular. | Thank you for your comment. The table of signs and symptoms suggesting alternative diagnoses is already given in the full version of the guideline. |
| SH | Alder Hey Childrens NHS Foundation Trust | 15 | Full | General | | I was very surprised not to find a Consultant Paediatric Surgeon among the Committee members. Whilst intussusception is mentioned, in my practice in PICU I have managed extremely ill children who have had missed appendicitis, a more difficult diagnosis in young children and children with other surgical conditions such as those associated with ischaemic bowel who have been treated by Paediatricians as having severe gastroenteritis prior to a surgical diagnosis being considered. | Thank you for your comment. This guideline is intended to help healthcare professionals in the management of children with gastroenteritis and the committee was constituted on that basis. The paediatricians were well aware of the range of other conditions that might cause diarrhoea. We consider that those matters are highlighted in the diagnosis chapter. |
| SH | AMM | 1 | Full | General | | *E.Coli* O157 should be written as such The O is a capital letter not a numeral as written in the document | Thank you. The error has been corrected. |
| SH | AMM | 2 | Full | General and p7 | | Ideally *Escherichia coli* should be written in full and the shortened form given and then used from then on. Both of these should be in italics. Suggest put the abbreviation with the full name on the Abbreviations page ie page 7 for clarity | Thank you this has been revised. |

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| SH | AMM | 3 | Full | 2.1,2.2 3.2.1 | | Please add Perform stool microbial investigations if you suspect there are linked cases outside the immediate family to identify a possible outbreak of gastroenteritis. | Thank you. If an outbreak is suspected, it has been recommended to notify public health authorities and act on their advice. The actions might not be limited to performing stool microbial examination only. |
| SH | AMM | 4 | Full | 2.1 2.2 3.2.1 | | Suggest add :Consider performing stool microbiological investigations if the child is a neonate. | Thank you. We were unclear as to why this suggestion was proposed. |
| SH | British Homeopathic Association | 1 | Gener al | General | | There is no mention of positive research evidence in homeopathy for diarrhoea. These papers are cited and meta-analysed in: Jacobs J, Jonas WB, Jimenez-Perez M, Crothers D. Homeopathy for childhood diarrhea: combined results and metaanalysis from three randomized, controlled clinical trials. *Pediatric Infectious Disease Journal* 2003; **22**: 229–234. | Thank you for bringing this paper to our attention. This has been included with another more recent publication in section 8.4 on alternative and complementary therapies. |
| SH | BSPGHAN | 1 | Full | | | Although the overall proposal is good, did not feel there needs to be a clear implementation plan developed for the guidelines and co-ordination with health professional groups such as GPs, Accident and Emergency groups, Paediatrics | The management of gastroenteritis in children is multifaceted and changing. New treatments (anti-emetic, antidiarrhoeal drugs, probiotics) and management strategies (clinical assessment of dehydration severity, rapid IV rehydration) are being proposed by other sources, whose roles have not been properly evaluated. This guideline has systematically examined the evidence on these topics (and other relevant topics), and developed clear and succinct statements which have to be shared with healthcare professionals across the UK. A formal implementation plan is essential and is |

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| | | | | | | | currently under development with NICE. |
| SH | BSPGHAN | 2 | Full | 2.1<br><br>Table 4.6. | 34 | The comment" combination of features must be present to determine a diagnosis of shock"- this needs to reviewed with clearer guidance re number of features, prioritizing features- quite ambiguous | Thank you for your comment. This wording has been amended. Those with shock will have one or more of the symptoms and signs presented in the table. |
| SH | BSPGHAN | 3 | Full | 2.1 | 35 Line 20 | Uncertain how hypernatraemic dehydration can be confirmed without undertaking venesection | Thank you. Hypernatraemia might be suspected on the basis of clinical manifestations – see recommendations on assessment of dehydration and shock. It might also be identified on blood testing for children commencing IVT who are subsequently changed to ORT to complete rehydation. |
| SH | BSPGHAN | 4 | Full | 2.1 | 35 Line 22 | Where is the evidence for 50ml/kg of ORS as standard replacement therapy | Thank you. This recommendation is a consensus decision of the GDG based on clinical experience and expert advice. Kindly see the GDG translation in section 5.3 (Oral fluids) for a detailed discussion. |
| SH | BSPGHAN | 5 | Full | 2.1 | 35 Line 22 | Maintenance fluids- is this per-oral or intravenous unclear in document | Thank you – a useful clarification. The recommendation has now been revised to make this clearer. |
| SH | BSPGHAN | 6 | Full | 2.2 | 41 Line46-48 | Would like to see the evidence, critical review or reasons for recommendation for no swimming for 2 weeks and staying off school/nursery for 48 hours post D+V | Thank you. These recommendations are taken from guidelines commissioned by the Department of Health. Kindly see the footnote for the relevant references. |
| SH | Department of Health | 1 | NICE | 1.2.1.2<br><br>& table 1 | 6 | In our opinion, the language, used in assessment (1.2.1.2 & table 1), should be similar to that used in the NICE *Feverish* | Thank you. The revised version of the table refers to the child's |

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| | | | | | | *Illness Guideline CG47,* as cases may overlap the two guidelines. In particular, *CG47* does not use the term lethargy, but describes responses to social cues and stimulation. We feel that this could enable assessors, particularly remote assessors, to obtain more precise information. | responsiveness and so is similar to the NICE feverish illness guideline in that respect. |
| SH | Department of Health | 2 | NICE | 1.8.2.1,<br><br>bullet point 5 | 23 | We would like to query whether there really is good evidence to support bullet point 5, return to school or care facility 48 hours after the last episode of diarrhoea and/or vomiting. In our opinion, this could have an impact on those with young children, who are at work. | These recommendations are taken from guidelines commissioned by the Department of Health:<br>Health Protection Agency. *Guidance on Infection Control In Schools and other Child Care Settings*. London: HPA; 2006 [www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947358374]<br>PHLS Advisory Committee on Gastrointestinal Infections. Preventing person-to-person spread following gastrointestinal infections: guidelines for public health physicians and environmental health officers. *Communicable Disease and Public Health* 2004; 7(4):362–84. |
| SH | Neonatal & Paediatric Pharmacists Group (NPPG) | 1 | Full | general | | The guidance is excellent | Thank you. |
| SH | Neonatal & Paediatric Pharmacists Group (NPPG) | 2 | Full | general | | It should be pointed out that ORS are available without a prescription and can be obtained from a community pharmacy along with professional advice. | Thank you for your comment. The mode of access to therapies has generally not been included as part of the guideline. |
| SH | Newham University Hospital NHS Trust | 1 | Full | Generalt | | Overall, we support the simple method of calculating dehydration and the oral fluid regime | Thank you for your comment. |

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| | | | | | | and speed of ORT. It is clear and easy to follow and implement | |
| SH | Newham University Hospital NHS Trust | 2 | Full | 1.5 | 29 Line 29 | Emergency Department Physicians should be specifically mentioned, as mentioned elsewhere in the text see high proportions of cases and contribution to care equal to GP and paediatricians | Agreed and appropriate change made. |
| SH | Newham University Hospital NHS Trust | 3 | Full | 2.1 | 34 Line 3 | This summary list excludes many of the indications for stool culture that are elsewhere in the text, which is confusing when reading – would add foreign travel, recent antibiotics, diagnostic doubt, and diarrhoea not improved in 7 days (+/- any child being admitted) | Thank you. There are two separate recommendations on microbiological investigations and they are with different indications – kindly see the complete list for further clarification. The given recommendation is one of the key ones and hence has been given separately. |
| SH | Newham University Hospital NHS Trust | 4 | Full | 2.1 | 35 Line 22 | mL is correct abbreviation? | Thank you. Both 'ml' and 'mL' are correct – we have used 'mL'. |
| SH | Newham University Hospital NHS Trust | 5 | Full | 2.2 | 39 Line 30 | Not clear – 'develops signs of shock or is still dehydrated after 4 hours ORT' perhaps. | Thank you for your comment. An appropriate amendment has been made. |
| SH | Newham University Hospital NHS Trust | 6 | Full | 2.2 | 39 Line 33 | No comment made as to whether you advise deducting boluses from maintenance, or giving in addition. Helpful to clarify. Also severe dehydration vs shock may be difficult to determine – risk of too rapid correction if the former and no upper limit on boluses. Should there be more guidance here (as per 30 mL/kg limit for DKA)? | Thank you for your comment. It is clear from the recommendation that maintenance fluid is to be given in addition to the boluses in those with clinical features of shock.<br><br>The recommendation is to administer 20 ml/kg and repeat this once if there are persisting features of shock. |
| SH | Newham University Hospital NHS Trust | 7 | Full | 2.2 | 39 Line | Should we also replace 10 mL/kg after each large vomit? | Thank you. The GDG considered your comment but decided to recommend |

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| | | | | | | | additional fluids to those passing large watery stools only. |
| SH | Newham University Hospital NHS Trust | 8 | Full | 2.2 | 39 Line 44 | Seems to conflict with NPSA and the discussion later in the text – helpful to distinguish from hypernatraemia from outset (0.9% saline) and iatrogenic hypernatraemia developing from treatment (presume this is where you advise switch to 0.45%) | Thank you. The recommendation states change to 0.45% saline "if hypernatraemia develops". This is not in conflict with NPSA. |
| SH | Newham University Hospital NHS Trust | 9 | Full | 2.5 | 44 Flow chart | In 'clinical dehydration' middle columns, 'absence of' and 'presence of' do you mean both or either of the signs listed? The boxes below have identical content except for the last point – might be clearer if advice in single box that splits for last point<br>'consider blood gas' – this might be better as 'always do initial blood gas, continue monitoring if abnormal or clinical signs acidosis or deterioration' (otherwise can't institute therapy change that follows) | Thank you. The two boxes have been combined as per your suggestion.<br><br>Your comment is appreciated. A new recommendation on measuring venous blood acid base status has now been drafted. |
| SH | Newham University Hospital NHS Trust | 10 | Full | 3.1 | 46 Line 22 | The definition should mention that this is an acute change, as explained in the text | Thank you. The definition is of diarrhoea and not of acute diarrhoea as in gastroenteritis. Nevertheless we have revised the text to make this distinction clearer. |
| SH | Newham University Hospital NHS Trust | 11 | Full | 4.1 | 64 Line 28 | Defining 'at risk' as > 2 vomits gives a very low threshold for advising face to face assessment (later in text), in the absence of any other worrying features | Thank you for your comment. This recommendation has been amended |
| SH | Newham University Hospital NHS Trust | 12 | Full | 4.1 | 69 Line 22 | Strongly support this | Thank you for your comment. |
| SH | Newham University Hospital NHS Trust | 13 | Full | 4.1 | 71 Table 4.6 | It might make sense to order the list within each box in terms of increasing severity ie milder features at the top of each box, red flags at the bottom | Thank you for your comment. The GDG considered this. However, the decision was to present details in the |

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| | | | | | | | sequence normally assessed on clinical examination. |
| SH | Newham University Hospital NHS Trust | 14 | Full | 4.2 | 79 Line 33 | Indications for investigation – should be done for any child requiring iv therapy, not just if shocked eg failure of ORT | Thank you for your comment with which we agree. Appropriate changes have been made in the recommendation. |
| SH | Newham University Hospital NHS Trust | 15 | Full | 5.4 | 93 Line 33 | Clarify as before | Thank you. The recommendation has been revised for clarity. |
| SH | Newham University Hospital NHS Trust | 16 | Full | 5.4 | 98 Line 1 | Or vomit? As before | Thank you. The GDG decided to recommend additional fluids to those passing large watery stools only. |
| SH | Newham University Hospital NHS Trust | 17 | Full | 5.4 | 98 Line 4 | Emphasise need for initial vbg and ongoing monitoring if unwell or results abnormal, as before | Your comment is appreciated. A new recommendation on measuring venous blood acid base status has now been drafted. |
| SH | Newham University Hospital NHS Trust | 18 | Full | 5.4 | 98 Line 5 | Again, seems to conflict with NPSA advice and text from wording | Please see response to your above comment number 8.<br><br>The recommendation states change to 0.45% saline "if hypernatraemia develops". This is not in conflict with NPSA. |
| SH | NHS Direct | 1 | NICE | | 6-7 | Some of the face to face assessment symptoms may be assessed fairly well by the parent/carer, ie: normal breathing pattern, normal heart rate, no sunken eyes, normal fontanelle and their answers may well help to give secondary | Thank you. A separate recommendation on symptoms has already been drafted. |

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| | | | | | | evidence about dehydration. | |
| SH | NHS Direct | 2 | NICE | | 8 | This is a very small point but is the "fruit juice" referred to made from whole fruit or is it referring to fruit squash/flavoured drinks? Parents/carers often want this information clarifying when given as care advice as many children will not drink plain water. | Thank you. The GDG did not recommend fruit juices and carbonated drinks in any form. This has been further clarified in the recommendations 1.3.1.1, 1.3.2.2, and 1.4.1.1 |
| SH | NHS Direct | 3 | General | general | | Content considered by NHS Direct, excellent. | Thank you. |
| SH | RCPCH | 1 | Full NICE | General | | This guideline is straight forward and simple. It is well structured and fits in well with the other guidelines on UTI and fever and is supported by the British Association of General Paediatricians. There are no real changes from common practice and no new concepts introduced. The main change of emphasis is that of classification of dehydration of 'not dehydrated', 'dehydrated' and 'shock' which is practically what most people do and so this is now an acknowledgment of this. It also makes the fluid guidelines simpler. However, this will not be in line with the recent NPSA recommendations prescribing fluid in children (and banning hypotonic fluids use) where there is a fluid calculation section based on percentage dehydration. | Thank you for your comment. Following GDG discussion with the NPSA, this chapter has been modified and the recommendation and key research recommendation amended. |
| SH | RCPCH | 2 | Full NICE | General | | The community face to face assessment section and the section on parent information were welcomed and read well. | Thank you. |
| SH | RCPCH | 3 | Full | General | | Rotavirus immunisation recommendations could be included – or at least the controversy and evidence discussed. | Thank you. This is outside the scope of this guideline. |
| SH | RCPCH | 4 | Full | 1.1 | 26-27 | In the introduction the guidelines talk about the global impact of D&V in the developing world, | Thank you. Appropriate amendments |

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| | | | | | | which while important, may be confusing. Presumably NICE guidelines are accessible to people in developing countries where management may be very different: it should be made clear that this is for UK population. | have been made. |
| SH | RCPCH | 5 | Full<br><br><br><br>NICE | 2.1 | 34-35 and 71<br><br>s 6-7 and 14 15 | The guideline implies that the fontanelle may be used to indicate dehydration up to 18 months. Some clinicians have expressed the that view it is fairly useless over 6 months even if it's not fully closed although it is not clear whether this is based upon evidence or clinical experience. | Thank you. The feature on fontanelle has now been removed from the table. |
| SH | RCPCH | 6 | Full | 4.2 | 73 | The is no controversy or disagreement about role of investigations | Thank you for your comment. |
| SH | RCPCH | 7 | Full<br><br><br><br>NICE | 2.1 | 34-35 and 71<br><br>6-7 and 14-15 | There are mixed views on red flags. Some clinicians like them and some don't – for those that do like them they could be developed further and emphasised more as this is the section most people will look at. | Thank you. We agree. The use of red flag was a key decision. Their importance is highlighted throughout the recommendations. |
| SH | RCPCH | 8 | Full | 2.2 | 39 | The most challenging part of the guideline is the advice that IV fluids should only be given if in 'shock' or deteriorating despite ORS. Drips are put up on wards all the time on children who are not that ill. The reason is often that there is no parent to sit with the child and offer frequent drinks, and the nurses are too busy. To make this guideline more realistic, perhaps it should include a provision for the use of IV fluids, at the clinicians' discretion, in clinically dehydrated | Thank you for raising this very practical point which the GDG considered. Although, as you point out, there are logistic/resource implications to offering sufficient ORS to dehydrated children, the GDG wanted to make a strong recommendation to prevent unnecessary IVT. The GDG considered that an amendment for the use of IV |

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| | | | | | | children in situations where inadequate volumes of ORS are being offered. | fluids, at the clinicians' discretion, would not be appropriate. |
| SH | RCPCH | 9 | Full | 2.5 | 44 | Flow pathway for fluid management does not appear to be in the NICE summary. | Thank you. This will be not be added to the NICE version, but will be in the Quick Reference Guide. |
| SH | RCPCH | 10 | Full | General | | How does the NICE guideline define failure of NGT? - further weight loss, deterioration of signs, persistent vomiting child (which will be the reason why they were there not because of the NGT) | Thank you for your comment. This is implicit in the recommendation on indications for IV therapy. |
| SH | RCPCH | 11 | Full | General | | ORAL Rapid Rehydration therapy needs to be discussed further (as per American Academy Pediatrics reference 5 recommendations) i.e. 25ml/kg per hour for the first 4 hours. Rapid IV Therapy has been acknowledged in the research recommendations but is clearly being used in some centres (Schutz J J. *Paediatrics and Child Health* 2008;44:560-563) but needs further discussion. We suggest a section on rapid rehydration therapy. | Thank you for your comment. The AAP 1996 recommendations suggested that administration of 100ml/kg ORS solution during the first four hours in children with moderate (6-9%) dehydration. This is not in keeping with our recommended strategy for assessing and treating dehydration. The GDG decided that accurate assessment of the 5 dehydration was likely to be unreliable hence, the strategy proposed. All clinically dehydrated children should be assumed to be 5% dehydrated in the first instance and treated accordingly. Those in whom the fluid deficit was greater than 5% would receive more fluid on the basis of periodic reassessment. This strategy is is discussed at length in the relevant GDG translation.<br><br>The increasing usage of various IV |

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| | | | | | | | repaid rehydration protocols is also discussed in the relevant translation. A research recommendation on this important topic was made. |
| SH | RCPCH | 12 | Full | General | | Changing practice from IVI to NGT seems still to be an issue (see reference above) and a section on '*from recommendation to implementation'* would be welcomed (as it would in all guidelines) in this guideline. | Thank you for your comment. Such a section is outwith the remit of the GDG. |
| SH | RCPCH | 13 | Full | General | | Hypoglycaemia reported in 9% of children with dehydration, but only checking blood glucose in children who are requiring IVT, when guideline as a whole recommends treating all children other than those shocked with ORS. Should there be the recommendation to check a bedside glucose in most children if we know that almost 10% will be hypoglycaemic? Was the evidence in relation to this issue reviewed. | Thank you. One study reported relatively mild hypoglycaemia (>2.2) in 8% of children treated with IV fluids for dehydration. In another study of moderately to severely dehydrated children only 1/119 children was said to have been hypoglycaemic. The GDG did not think it was appropriate to recommend routine screening for hypoglycemia on the basis of this conflicting evidence. |
| SH | RCPCH | 14 | Full NICE | General | | There appears to be no mention of weight in the assessment of a child with gastroenteritis. The Guideline group have elected not to use "percentage dehydration" as an assessment option which is reasonable given the traffic light system and evidence presented. However were a child to return to secondary care where weight measurement is easily available this is an important piece of additional information which is unhelpful if a weight is not performed on the initial presentation. In addition, any determination of % dehydration will in practise be based on pre-illness and current weight. | Thank you. Although, the GDG recognised that if an accurate and very recent weight record was available prior to the onset of the diarrhoeal illness this might provide a guide to percentage weight loss. The reliability of this approach was not certain however, and the GDG doubted that it was often relied upon. For that reason it was considered that the child's state of hydration should be assessed clinically in each case. |

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| SH | RCPCH | 15 | NICE | 1.2.1.3 | | Signs of symptoms of other potentially more serious disease processes are not included in the table. Although not the primary purpose of the table a sole focus on features of dehydration on a child who presents with vomiting may lead to other processes being missed. Children who have brain tumours or meningitis have been sent home on the primary presentation after having completed a fluid trial. Can we also confirm that the title of the guideline will be D & V in children with gastroenteritis and not just D&V in children. Likewise an asterix in the table to remind clinicians that if other symptoms suggestive of alternative disease process are present, then these guidelines do not apply. | Thank you. We agree regarding the title and this ahs been amended. The primary purpose of the table is to help health care professionals in assessing the severity of dehydration, not to provide a differential diagnosis.<br><br>Signs and symptoms suggestive of an alternative diagnosis have already been provided in a separate recommendation . |
| SH | RCPCH | 16 | Full NICE | General | | Although specific management advice is given it is not entirely clear when an escalation of care is required. i.e primary to secondary care. | Thank you. This is explicit in the recommendations made in the chapter 'Escalation of care'. |
| SH | RCPCH | 17 | NICE | 1.3.3.2 | 17 | The guideline states to give a specified amount of ORS over a four hour period and monitor response regularly. This implies the child should remain in a hospital setting. The four hour target in Emergency Departments would make it impossible for this standard to be met. | Thank you. We do not agree that this implication is made, as ORS can be given in the community. |
| SH | RCPCH | 18 | NICE | 1.2.1.3 | 14 | The inclusion of increased thirst as an amber category is potentially confusing. Although the evidence may indicate it is a sign of dehydration in the absence of other signs or symptoms it may cause confusion (a child who appears very well and is just drinking more has an amber warning sign) and potential over referral. It is relatively uncommon symptom in the under 5 age group. The inclusion of normal signs in the amber category (warm hands and feet and | Thank you. The GDG considered this and have deleted increased thirst from the list of symptoms. However, the other two features have also been revised. |

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| | | | | | | normal skin colour is also confusing) | |
| SH | RCPCH | 19 | NICE | | 4 | Rather than referring to the drugs Summary of Product Characteristics, the reader would be more familiar with BNFC. | Thank you, a footnote has been added on the products available in the UK. |
| SH | RCPCH | 20 | NICE | | 5 | The sentence should complete 'due to gastroenteritis.' | Thank you. |
| SH | RCPCH | 21 | NICE | | 7 | Annotation to table 1, b does not did | Thank you appropriate changes have been made. |
| SH | RCPCH | 22 | NICE | | 8 | The reference to 'low osmolality ORS' has the potential to confuse the reader. This should be clarified by stating that UK available rehydration salts are of low osmolality compared with the WHO formulation, and defining the osmolality that is meant by "low".<br><br>The is a typo- encourage *the child* to drink. | Thank you. A footnote has been added on the products available in the UK. |
| SH | RCPCH | 23 | NICE | | 8-9 | The reference to 15mls per kilogram may be problematic to those in primary care, where access to weighing may not be available at the time of giving advice. Similarly parents are unlikely to find this useful. The BNFC gives an age related volume. NICE will have considered this but the College would suggest that this latter method is easier to use (similarly the recommendation (page 9) 5-10ml per kilogram passing a large stool has practical difficulties for parents. | Thank you. The GDG considered this, but were satisfied with their original wording. |
| SH | RCPCH | 24 | NICE | 1.1.2.4 | 13 | Bullet point 1 is unhelpfully vague | Thank you. Though this might be considered vague, the GDG thought this to be important. |
| SH | RCPCH | 25 | NICE | 1.1.2.7 | 13 | Presumably this is for Haemolytic Uraemic Syndrome but the authors should not assume that the average reader has this knowledge. | Thank you. Appropriate changes have been made as follows:<br><br>In children with *E. coli* O157:H7 infection, seek specialist advice on |

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| | | | | | | | monitoring for haemolytic uraemic syndrome. |
| SH | RCPCH | 26 | NICE | 1.2.1.4 | 16 | The College would suggest changing 'hypertonicity' to 'increased muscle tone' to avoid any confusion with 'hypertonic dehydration'. | Thank you this has been revised. |
| SH | RCPCH | 27 | NICE | 1.3.3.1 | 17 | Again the College would suggest clarification and referral to BNFC about how this applies to UK available ORS as opposed to WHO formulation. | Thank you. The products currently available in the UK have been detailed in a footnote. |
| SH | RCPCH | 28 | NICE | 1.3.4.4 | 18 | The guideline should consider the needs for maintenance or additional potassium.<br><br>The average practitioner may need advice about how to calculate 'maintenance fluids'.<br><br>There should be some guidance regarding how often to monitor serum electrolytes. | Thank you for your valuable comment regarding potassium supplementation.<br><br>Appropriate changes have been made. In the full version we have provided a working example of how to calculate the maintenance fluid to support implementation, rather than drafting a separate recommendation. |
| SH | RCPCH | 29 | NICE | 1.5.2 | 20 | The term 'Appropriate antibiotic' is unhelpful. The guideline could be enhanced by simple advice for first line antibiotics for the bacterial diagnosis specified in the 5th bullet point of this paragraph | Thank you. We agree and have deleted the word 'appropriate'. |
| SH | RCPCH | 30 | NICE | 1.5.3 | 20 | More specific advice regarding foreign travel would help the reader | Thank you. The recommendation has been revised to seek specialist advice, but we cannot be more prescriptive than this. |
| SH | RCPCH | 31 | Full | General | 20 | The initial assessment of dehydration should also include<br>looking at anterior fontanelle,(under 1yr), level of consciousness, signs of shock and urine output | Thank you for your comment. The GDG thought that the present list is sufficient |
| SH | RCPCH | 32 | Full | General | 58 | A second infection(viral or bacterial)during that | |

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| | | | | | | 8weeks is not mentioned. | Thank you for your comment. |
| SH | RCPCH | 33 | NICE | 1.3.3.2 | 17 | It is necessary to indicate how long to rehydrate in hypernatraemia (Should this be12 hours rather than 4?). | Thank you. A separate recommendation has been drafted for the IVT management of a child presenting with hypernatraemic dehydration. Additionally, advice has been given for the child developing hypernatraemia during IVT. |
| SH | RCPCH | 34 | NICE | 1.3.4.1 | 17 | An additional red flag 'if not tolerating ORS' should be considered. | Thank you for highlighting this. This has now been added as the third bullet point under "indications for IVT". |
| SH | RCPCH | 35 | NICE | 4.1 | 25-26 | There is some need to discuss whether shocked children would be under-rehydrated at 50ml/kg and should be preferably assessed as 10% and thus receive 100ml/kg rehydration. It is not clear in the guidance whether this is taken into account. | We agree with your suggestion and have revised the recommendation on IVT for shocked children (1.3.3.4). The first bullet point of the recommendation now reads as<br>"for those who were initially shocked and received bolus fluid resuscitation, give 100 ml/kg as fluid deficit replacement over 6 hours in addition to maintenance fluid requirements". |
| SH | RCPCH | 36 | NICE | General | | The guideline focuses on clinical assessment of dehydration, but the most accurate is actual weight comparison which allows for a more accurate calculation of dehydration and thus calculation of fluid requirements (if for example child weighed 1 week ago at 10kg and now wieghs 9kg on admission, we know that they have lost 10% due to dehydration, and would give them 100ml/kg rather than 50ml/kg rehydration). | Thank you. Although, the GDG recognised that if an accurate and very recent weight record was available prior to the onset of the diarrhoeal illness this might provide a guide to percentage weight loss. The reliability of this approach was not certain however, and the GDG doubted that it was often relied upon. For that reason it was considered that the child's state of hydration should be assessed |

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| | | | | | | | clinically in each case. |
| SH | RCPCH | 37 | NICE | Key Priorities | 8 | Fluid management: point No. 2: does the evidence support the recommendation that if a child is vomiting persistently, the optimal management would be to continue ORS rather than admit the child to hospital? If so, needs referencing. If not, and this is a consensus decision, this too needs to be stated. | This was a consensus decision and has been discussed in detail in the last paragraph before the recommendation (section 5.3 on Oral fluids). |
| SH | RCPCH | 38 | NICE | Key Priorities | 8 | The first sentence of Fluid management: point No. 3: Use of IV fluid therapy for dehydration should include the term 'impending shock'. | Thank you for your comment with which we agree. The sentence has been revised to 'if shock is suspected or confirmed'. |
| SH | RCPCH | 39 | NICE | 1.1.2.7 | 13 | The sentence needs to be changed slightly: monitor FBC, urea and electrolytes in all children requiring admission to hospital with gastroenteritis (this is common practice). | Thank you. The GDG considered your comment, but were satisfied with the recommendation already made. |
| SH | RCPCH | 40 | NICE | 1.2.2.1 | 16 | The sentence should be changed current agreed practice: Do not routinely perform blood biochemical testing unless the child requires admission to hospital. | Thank you.The GDG considered your suggestion but decided not to amend the recommendation. |
| SH | RCPCH | 41 | NICE | 1.3.4.3 | 18 | The first sentence should contain the following: give another rapid infusion of 20mls/kg Normal saline and consider referral to tertiary services. The infant can enter easily into pulmonary oedema from IV fluids of 40mls/kg or more if given rapidly, therefore referral to tertiary services i.e. PICU is prudent. | Thank you for highlighting an important point. Appropriate changes have been made in the recommendation. |
| SH | RCPCH | 42 | Full | 4.2 | 26 | With the recent NPSA safety alert on intravenous fluids in children, should 0.9%Nacl/5% dextrose be the recommended fluid? | Thank you. Section 4.2 related to lab investigations. We were uncertain of the context of your comment. This guideline is in keeping with NPSA advice. |

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| | | | | | | | The recommended fluid for IVT is an isotonic solution (0.9% sodium chloride or 0.9% sodium chloride with 5% glucose) for both fluid deficit replacement and maintenance. This is in line with the NPSA recommendations. Kindly see the GDG translation of section 5.4 on IVT for a detailed discussion. |
| SH | RCPCH | 43 | NICE | General | | The infants who were of low birth weight are mentioned specifically in several sections including fluid management, guidance etc however many babies of low birth weight behave like normal babies when they are 2 years and over. It depends on what neonatal problems they encountered but birth weight by itself does not single them out as a special category in the case of gastroenteritis. | Infants are defined as children younger than 1 year. This recommendation therefore refers to only this group. We fully agree that this recommendation does not refer to children over 1 year of age. |
| SH | RCPCH | 44 | NICE | General | | When giving the specified amount of oral rehydration solution it would be better to state what the maintenance volume should be in addition to 50ml/kg. This could be done by adding the fluid (volume / kg body weight / day) chart to the guideline so that the reader could refer to it whenever maintenance volume is mentioned. It makes the guideline more practical to the person referring to it in the clinical scenario. | In the full version we have provided a working example of how to calculate the maintenance fluid to support implementation, rather than drafting a separate recommendation. |
| SH | RCPCH | 45 | NICE | | | The guideline reads well and the clinical assessment of dehydration chart was easy to follow. | Thank you. |
| SH | RCPCH | 46 | Full | 2.2 | 37 Line 14 | It seems inconsistent to offer advice re measurement of CRP in immuno-compromised children, when they were specifically excluded | Thank you. Immuno-compromised children are not excluded from the scope. They have been considered |

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| | | | | | | from the scope. If you are going to comment on their management, then it will need more than this simple statement. | separately under antibiotic therapy also. However on revisiting, this recommendation has now been removed. |
| SH | RCPCH | 47 | NICE | general | | There appears to be considerable duplication between the "implementation" and the recommendations. Would it be more fruitful to focus on any changes in practise in the "implementation" section? | The key priorities for implementation (KPI's) are 5-10 recommendations selected by the GDG which are likely to have the biggest impact on the patient care and/or outcomes in the NHS as a whole, or promote equality and patient choice. Hence they will be duplicated. For implementation, a separate plan is also being developed which will focus on changes in practice in detail. |
| SH | Royal College of Nursing | 1 | Full | General | | The RCN welcomes this draft guideline. It is comprehensive. There are few areas that may require clarification to make easier to read and/or avoid confusion. | Thank you. |
| SH | Royal College of Nursing | 2 | Full | Intro | 3 | Paragraph 2 *"most children with gastroenteritis do not require admission to hospital; many are treated as in-patients each year*". This is a bit unclear; would it be better to word this as "Although many children are treated as in-patients each year most children do not actually require admission to hospital and could be managed safely and effectively at home"? | Thank you for your comment. |
| SH | Royal College of Nursing | 3 | Full | Patient- Centred Care | 5 | Paragraph 1 *"Treatment and care should take into account children's needs and preferences and those of their parents and carers"*. Would it be better to word this "Treatment and care should take into account both the needs and preferences of children and their parents and carers"? | Thank you for your comment. |
| SH | Royal College of | 4 | Full | Table 1 | 6 | "Clinical Dehydration" category reads as "*With* | Thank you. This sentence has now |

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| | Nursing | | | | | *worsening dehydration clinical manifestations may be expected become more numerous and severe*." Could be reworded to read "With worsening dehydration clinical signs and symptoms may increase in both frequency and severity"? | been deleted and the table revised. |
| SH | Royal College of Nursing | 5 | Full | Table 1 | 6, 7 | This table seems confusing as some of the symptoms displayed in clinical dehydration can also be evident if the child is shocked. Although this is made clear in some areas (eg tachycardia is present in both columns) it is not made clear in all (eg. Decreased urine output). | Thank you. We do not think that any significant apparent conflict remains in the revised table. |
| SH | Royal College of Nursing | 6 | Full | Text after table 1 | 7 | Explanation for 'b' reads as ", *but did not have sufficient diagnostic utility to do so in isolation*". Should this read "The presence of this symptom may help to rule out dehydration but should not be used in isolation as a diagnostic indicator"? | Thank you. The footnotes have now been removed. |
| SH | Royal College of Nursing | 7 | Full | Fluid Management | 8 | Before diamond bullet points relating to the use of ORS it may be useful to include the word "including" to reaffirm that the previous points relate specifically to this group of children. | Thank you for your comment. We could not find the relevant text in the full guideline to address your query. |
| SH | Royal College of Nursing | 8 | Full | Fluid Management | 8 | Second block of text beginning "In children....."; should the last line read ORS? At present it reads as ORT? If this is meant to indicate therapy and not solution as one suspects then the term should be cited in full before use of the abbreviation to avoid confusion. | Thank you for your comment. We could not find the relevant text in the full guideline to address your query. |
| SH | Royal College of Nursing | 9 | Full | General | | Throughout the document there is intermittent use of abbreviations and full terminology for both "oral rehydration solution" and "oral rehydration therapy". Some people may find this quite confusing when reading these guidelines. Would it be better to provide the full term for each at the outset and thereafter to use only the abbreviations? | Thank you. Appropriate changes have been made in both the NICE version and the full guideline. These terms have also been defined in the glossary of both the versions. |

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| SH | Royal College of Nursing | 10 | Full | General | | Diarrhoea and vomiting can be both over treated and under treated medically. From an under treatment point of view, we believe that bloody diarrhoea is considered rare, for this very reason it is suggested that a stool specimen should be sent for e-coli 0157 test.<br><br>We would recommend that if this is the case, bloods should be taken for U & Es and FBC so that these children are referred early if they have Haemolytic Uraemic Syndrome (HUS). We appreciate this is a small number however, the morbidity and mortality risk of this group is very high if referral is late to renal units. | Thank you. We appreciate your concern regarding high mortality and morbidity associated with HUS. However the management of HUS will vary from child to child depending on the clinical features/complications, and it should be done in consultation with a specialist. This has now been reflected in the revised recommendation as below.<br><br>'In children with *E. coli* O157:H7 infection, seek specialist advice on monitoring for hemolytic uraemic syndrome'. |
| SH | Royal College of Pathologists | 1 | FULL | General | 1 | Title should refer to children under five. | Thank you. This has been amended. |
| SH | Royal College of Pathologists | 2 | FULL | 1.3 | 28, Ln 35 | Suggest: 'acute diarrhoea …**thought to be** due to gastroenteritis | Thank you. The guideline is specifically on the diagnosis, assessment and management of diarrhoea and vomiting caused by gastroenteritis. We have considered your suggestion but on reflection prefer to stay with the current phrasing for clarity. |
| SH | Royal College of Pathologists | 3 | FULL | 1.4 | 23, Ln 23 | It is not wise to exclude Public Health Issues totally from the scope, though I see how NICE does not want to get drawn into the issue of complex preventive and hygiene measures. Later in the document you do acknowledge the importance of notifying public health authorities of outbreaks, for example. | Your comment is well appreciated. Though Public Health issues are vital for this topic, it was not included in the agreed scope of this guideline. Nevertheless a child presenting with diarrhoea and vomiting could be the index case of an outbreak and the GDG agreed to emphasize the |

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| | | | | | | | importance of notifying public health authorities in such situations. |
| SH | Royal College of Pathologists | 4 | FULL | 3.2.1 | 59 | Suggest you include 'suspected outbreak' as a situation when stool microbiological investigations should be carried out. | Thank you. If an outbreak is suspected, it has been recommended to notify public health authorities and act on their advice. The actions might not be limited to performing stool microbial examination only. |
| SH | Royal College of Pathologists | 5 | FULL | General | | While I note your desire to avoid public health issues, clinical practitioners need to be aware of the public health importance of infectious diseases, and especially the legal implications. Gastroenteritis due to Salmonella, Campylobacter, Yersinia and many other pathogens is usually foodborne, yet nowhere in the document can I find mention of the fact that food poisoning, however diagnosed, is statutorily notifiable by the diagnosing clinician, under Public Health Law in the United Kingdom. | Thank you. The public health responsibilities of the clinicians are acknowledged (put in ref to line from new draft).<br>Under recommendations under laboratory investigations clinicians should inform the PH authorities of disease outbreaks. |
| SH | Royal College of Pathologists | 6 | FULL | 7.2.1 | 115; Line 36 – Line 39 | The second and third sentences in this paragraph (concerning the duration of Salmonella excretion with ampicillin) appear to be contradictory. | Thank you for your comment. Two outcomes were recorded and the text has been amended for greater clarity. |
| SH | Royal College of Pathologists | 7 | FULL | 7.7 and 7.10 | 120 and 127 | The analysis, and dismissal, of the evidence for the use of Nitazoxanide seems thin. For example, I am not clear why the following was excluded from consideration: | Thank you for highlighting this study. It has now been included in the evidence overview and appropriate changes have been made in the translation in light of your comment. |

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| | | | | | | Beatrice Amadi, Mwiya Mwiya, John Musuku, Angela Watuka, Sandie Sianongo, Ayman Ayoub, Paul Kelly, **Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial,** The Lancet, Volume 360, Issue 9343, 2 November 2002, Pages 1375-1380,<br><br>The drug has recently been licensed by the FDA for use in children, and it is reasonable to assume the licensing process in the USA demands some evidence of efficacy.<br>The fact that the drug is not yet licensed in the UK should not preclude NICE advocating its use, if the evidence supports it. The statement that NICE does not recommend it because most cases recover anyway is rather weak and lame – the same could be said of many unpleasant infections, which will get better in most patients if you wait long enough. The diarrhoea of Cryptosporidiosis is typically prolonged, and as long as the child has diarrhoea they remain infectious to others and must be excluded from nursery, playgroups etc. A safe and effective treatment which shortens this period of exclusion and infectivity should not be lightly dismissed. | The GDG was nevertheless unconvinced that a recommendation to use nitazoxanide could be made at this time. |
| SH | Royal College of Pathologists | 8 | FULL | 7.10 | 124 - 127 | You do not mention that gastroenteritis due to Giardia should be treated with Metronidazole or Tinidazole. While this is typically a longer 'non-acute' illness, many patients do present to their doctor before two weeks of illness have elapsed. You do discuss other rarer parasitic infections, however. | Thank you for your comment. We have now included giardiasis in our recommendation on antibiotic therapy. |

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| SH | Royal College of Pathologists | 9 | FULL | 8.4 | 154-163 | You note that many of the studies of probiotics show benefit, yet because some of the studies are of poorer quality, and because they are not licensed in this country, this leads you to the conclusion that probiotics should not be recommended (yet). This is surely not logical, and seems excessively cautious. If a treatment is effective, or beneficial, it is surely the job of NICE to recommend it. This recommendation can then act as a driver to getting the treatment licensed. The scope of this guideline does not exclude unlicensed products. Furthermore, if somebody carries out a good study with a convincing demonstration of efficacy of a treatment, this should not be dismissed because somebody else has carried out a poor quality study in the same area. | Thank you. The decision that a clinical recommendation could not be made was based on a lack of satisfactory supportive evidence for specific probiotic agent administered using specific regimens. The GDG was impressed by the overall trend observed in favour its effectiveness, and therefore prioritized it as a key research recommendation.<br><br>We noted that these agents are not licensed, but the recommendation was in fact based on our examination of the evidence. The translation has been modified to clarify this point. |
| SH | Royal College of Pathologists | 10 | FULL | General | | The occasional advice to 'consider' various treatments should be avoided if at all possible. After all, doctors consider treatment options all the time – what people want from NICE is clear advice as to which is the recommended and better treatment option. | Thank you. While firm recommendations are generally given, the GDG recognised that health care professionals may need to take account of a range of variables when deciding whether certain recommendations apply to individual patients. The expression "consider" was therefore sometimes the best option. |

The following registered stakeholder organisations were also invited to comment, but did not respond.

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| Association for Continence Advice |
| Association of Psychoanalytic Psychotherapy in the NHS |
| Association of the British Pharmaceuticals Industry (ABPI) |

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| Barnsley Hospital NHS Foundation Trust |
| Barnsley PCT |
| Berkshire Healthcare NHS Trust |
| Boehringer Ingelheim Ltd |
| Bolton Council |
| Bournemouth and Poole PCT |
| Bradford & Airedale PCT |
| Breastfeeding Network, The |
| British Dietetic Association |
| British National Formulary (BNF) |
| Buckinghamshire PCT |
| Calderdale PCT |
| Cardiff and Vale NHS Trust |
| Chelsea & Westminster Acute Trust |
| CIS'ters |
| College of Emergency Medicine |
| Commission for Social Care Inspection |
| Connecting for Health |
| ConvaTec |
| Cornwall & Isles of Scilly PCT |
| Department for Communities and Local Government |
| Department of Health, Social Security and Public Safety of Northern Ireland |
| Derbyshire Mental Health Services NHS Trust |
| East Kent Coastal PCT |
| General Chiropractic Council |
| General Osteopathic Council |
| GlaxoSmithKline UK |
| Good Hope Hospitals NHS Trust |
| Greater Manchester West Mental Health NHS Foundation Trust |
| Harrogate and District NHS Foundation Trust |
| Health and Safety Executive |
| Health Protection Agency |
| Healthcare Commission |
| Home Office |
| Infection Prevention Society |
| Institute of biomedical Science |
| La Leche League GB |

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| Leeds PCT |
| Liverpool PCT |
| Luton & Dunstable Hospital NHS Foundation Trust |
| Maternity Health Links |
| Meat & Livestock Commission |
| Medicines and Healthcare Products Regulatory Agency (MHRA) |
| Medicines for Children Research Network (MCRN) |
| Mental Health Act Commission |
| Milton Keynes PCT |
| National Childbirth Trust |
| National Patient Safety Agency (NPSA) |
| National Pharmacy Association |
| National Public Health Service - Wales |
| National Treatment Agency for Substance Misuse |
| NHS Bedfordshire |
| NHS Clinical Knowledge Summaries Service (SCHIN) |
| NHS Kirklees |
| NHS Plus |
| NHS Purchasing & Supply Agency |
| NHS Quality Improvement Scotland |
| NHS Sheffield |
| Norgine Ltd |
| North Yorkshire and York PCT |
| Northwick Park and St Mark's Hospitals NHS Trust |
| Nottingham University Hospitals NHS Trust |
| PERIGON Healthcare Ltd |
| Queen's Medical Centre Nottingham University Hospitals NHS Trust |
| Royal College of General Practitioners |
| Royal College of Midwives |
| Royal College of Physicians London |
| Royal College of Radiologists |
| SACAR |
| Sandwell PCT |
| Sanofi Pasteur MSD |
| Sanofi-Aventis |
| Scottish Intercollegiate Guidelines Network (SIGN) |
| Scottish Nutrition & Diet Resources Initiative |

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| Sedgefield PCT |
| Sefton PCT |
| Sheffield PCT |
| Sheffield Teaching Hospitals NHS Foundation Trust |
| Shrewsbury & Telford Hospital NHS Trust |
| Social Care Institute for Excellence (SCIE) |
| South Central Ambulance Service NHS Trust |
| Staffordshire Ambulance HQ |
| The Phoenix Partnership |
| The Royal Society of Medicine |
| University College London Hospitals (UCLH) Acute Trust |
| Welsh Assembly Government |
| Welsh Scientific Advisory Committee (WSAC) |
| Western Cheshire Primary Care Trust |
| Western Health and Social Care Trust |
| Wiltshire PCT |
| Wirral Hospital Acute Trust |
| York NHS Foundation Trust |

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