National Institute for Health and Care Excellence

Medical technologies evaluation programme

GID-MT551 Prontosan for acute and chronic wounds

Consultation comments table

Final guidance MTAC date: 10 December 2021

There were 169 consultation comments from 16 consultees:

- 73 Comments from Healthcare professionals
- 72 Comments from the manufacturer
- 24 Comments from specialist organisation

The comments are reproduced in full, arranged in the following themes:

- Recommendations (comments 1 to 21)
- Technology (comments 22 to 38)
- Improved wound condition (comments 39 to 61)
- Clinical evidence (comments 62 to 143)
- Economic modelling (comments 144 to 150)
- Equality (comments 151 to 157)
- Inaccuracies (comments 158 to 169)

#	Consultee ID	Role	Section	Comments	NICE Response
Recommendations (n = 21)					
1.	1	Healthcare professional	Recommendations (section 1)	I do feel in part that the recommendations have missed the importance in their current form of the value of prontosan in wound care. Prontosan should not be 'marked down' due to various secondary dressings etc., and that Bellingeri soak times are relevant to clinical practice as we know clinical judgement is required. This should not be viewed negatively.	Thank you for your comment. Section 4.10 describes Prontosan being part of a bundle of care and the importance of consistent and appropriate wound care pathways for chronic wounds. Section 4.8 has since been amended to reflect the discussion about the relevance of the BWAT score to NHS practice.
2.	3	Healthcare professional	Recommendations (section 1)	Yes, I personally have seen good results when using prontosan on chronic leg ulcer wounds	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
3.	7	Healthcare professional	Recommendations (section 1)	No - please see my comments below (comment 71).	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
4.	7	Healthcare professional	Recommendations (section 1)	I feel the guidance should be more supportive of the use of prontosan as first line treatment for wound cleansing. Water and saline do not have any good evidence for use. Prontosan is used first line for all wounds in our podiatry department. It has the best evidence base and clinically it gives us the best results. I am currently undertaking a research project using prontosan solution and gel x and not one of the wounds I am treating which are all chronic diabetic foot ulcers have had any infections whilst using this regime. The wound beds are greatly improved due to the impact of the products on cleansing/desloughing and preventing biofilms.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
5.	9	Healthcare professional	Recommendations (section 1)	Seem a bit harsher than other product evaluations by NICE which resulted in a recommendation for use. Whilst I commend a rigorous	Thank you for your comment.

				approach the rules cannot be changed unless re applied to all previous applications	The evaluation was conducted according to NICE's published process and methods guide for medical technology evaluation. The committee's decision reflects the published scope, and it cannot be compared with interventions and comparators not listed in the scope.
6.	12	Specialist organisation	Recommendations (section 1)	the NWCSP agrees with the draft recommendations which are a fair response to the currently available research evidence .	Thank you for your comment.
7.	15	Specialist organisation	Recommendations (section 1) Are the recommendations sound and a suitable basis for guidance to the NHS?	No likely to encourage inappropriate and overuse which will increase cost and the likely hood of resistance. AMS would not be supportive of increased use.	Thank you for your comment.
	Recommendations – evidence				
8.	8	Healthcare professional	Recommendations (section 1.1)	The evidence for prontosan in more than sufficient to inform my clinical practice. We have include Prontosan in our wound care formulary due to this high level of evidence. the mix of chronic wounds in the evidence are representative of wounds i see in my daily community practice. the amount of RCT for Prontosan is a lot compared to a lot of other wound care products.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Please note that this is a single technology evaluation, conducted according to NICE's published process and methods guide for medical technology evaluation. The committee's decision reflects the published scope, and it cannot be compared with interventions and comparators not listed in the scope.
9.	2	Manufacturer	Recommendations (section 1.1)	In addition we would like to highlight that the EAC summarised on page 7 "despite weaknesses in the evidence (clinical and economic) the EAC considers that based on the current available evidence the use of Prontosan products as an option for chronic wound management is supported". We request this is reflected and addressed in the guidance	Thank you for your comment. The committee has carefully considered the evidence and concluded that Prontosan shows promise but that there is not enough high-quality evidence to

					support the case for adoption. Further research is also recommended. Please also note that although the EAC's assessment report is part of the information the committee will consider to reach a decision, the committee's final decision is independent.
10.	5	Healthcare professional	Recommendations (section 1.1)	Further research is always welcome, especially in the form of a longitudinal study. I feel the current level of evidence already meets my key criteria and outcomes. There is sufficient evidence for the informed use of both the gel and solutions.	Thank you for your comment. The committee has carefully considered the evidence and concluded that Prontosan shows promise but that there is not enough high-quality evidence to support the case for adoption. An RCT comparing Prontosan with saline or water in the NHS has been recommended. Please also note that as stated in the guidance when the technology is recommended for use in research, the recommendations are not intended to preclude the use of the technology but to identify further evidence which, after evaluation, could support a recommendation for wider adoption.
11.	6	Healthcare professional	Recommendations (section 1.1)	What about acute would that have risk of infection to prevent them becoming a chronic wound? Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust developed and implements a wound cleansing policy using prontosan on chronic wounds and acute wounds at risk of infection as 1st line in 2017. We have been able to achieve a 66% reduction in wound infection in our complex wound clinic using this principle. 2017 19/261 patients had a wound infection (7.3) and in 2020 2/78 patients had a wound infection (2.5%). The complex wound clinic review complex wounds including chronic wounds (more than 14 days old) e.g. leg ulcer, diabetic foot ulcers) and acute wounds at risk of infection e.g. surgical wounds, skin grafts.	Thank you for your comment. The EAC noted that there was only 1 comparative study (Saleh 2020) that presented results on infection for acute wounds. This study had a small sample size and used only 1 application of Prontosan. It reported significantly higher rate of infection following use of Prontosan. The committee considered this comment carefully but decided not to change the guidance.

12.	15	Specialist organisation	Recommendations (section 1.1)	Agree - very low quality evidence	Thank you for your comment.
	Recommendations – further research				
13.	8	Healthcare professional	Recommendations (section 1.2)	There are plenty of studies compared to saline, in particular the study from Italy which looks at wound management over 28 days which showed improvements vs saline.	Thank you for your comment. The committee considered this comment carefully but decided that there is not enough good quality evidence comparing Prontosan with saline or water.
14.	6	Healthcare professional	Recommendations (sections 1.2)	There is significant evidance for the use of prontosan which has been reflected in clinical practice. However further research is always welcomed i do not feel this is requires as the key outcome we have seen have been significant in all different wound types.	Thank you for your comment. Please see NICE's response to comment 10.
15.	2	Manufacturer	Recommendations (section 1.2; 4.11)	Please refer to comments in 4.5.	Thank you for your comment. Please see NICE's response to comments 38, 55, 56, 57.
16.	2	Manufacturer	Recommendations (section 1.2; 4.11)	There is strong clinical evidence supporting the use of Prontosan for wound condition. The committee have highlighted some of the issues in wound care in section 3.9 with regards to planning robust clinical study. To represent appropriate clinical use of Prontosan products, studies would need to be used prontosan according to the IFU – ie depending on wound condition. Any study would need to be designed in line with national guidance If the committee want to limit the study to Prontosan solution, then the chronic wounds need to be suitable for use with Prontosan solution alone, this may limit the external validity and generalisability of the study.	Thank you for your comment. Please see NICE's response to comment 10.
17.	2	Manufacturer	Recommendations (section 1.2; 4.11; 4.12)	We would highlight that these outcome measures were reported in the evidence provided and summarises by the company (page 353-354 in the company submission) and the EAC also report in detail on quality of life in their qualitative discussion (page 49-59 in the including tables 13-16).	Thank you for your comment. Quality of life was descriptively reported in 3 of the non-comparative studies. One study reported QoL outcomes in 43 people. The committee considered that there is a lack of high-quality comparative data on quality of life so agreed that other outcomes should include pain and wound

					odour, measured using patient-reported outcome measures (PROMs). The committee considered this comment carefully but decided not to change the guidance.
18.	5	Healthcare professional	Recommendations (section 1.2; 4.12)	Further research and RCT are always welcome and I think a longitudinal study would also be beneficial to allow the benefits to be seen across the healing and wound spectrums.	Thank you for your comment. Please see NICE's response to comment 10.
19.	13	Healthcare professional	Recommendations (section 1.2)	wounds should be followed up until healed however the use of prontosan accelerated wound healing reducing cost and nursing time.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
20.	15	Specialist organisation	Recommendations (section 1.2)	Agree but consider for direct comparison should have another active liquid as comparator. Water is considered effective and safe to use in cleansing (NICE)and is free. The use of Prontosan has an immediate cost implication. Multiple formats will increase confusion among staff, leading to inappropriate use. Agree with lack of evidence	Thank you for your comment. The committee has carefully considered this comment and decided that the comparator should be saline or water.
	Recommendations – rationale				
21.	2	Manufacturer	Recommendations (section 1.2)	Please see comments to 3.2 and review this sentence accordingly.	Thank you for your comment. The rationale is intended as a lay summary of the guidance. Changes were made in line with NICE plain English wording.
Technology (n = 17)					
22.	15	Specialist organisation	The technology (section 2.1)	Concerns that soak time is not adhered to due to time constraints	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Section 4.9 describes that Prontosan does not add to the appointment time if

					the soak is applied at the start of the appointment.
23.	15	Specialist organisation	The technology (section 2.3)	Been around since 2008, therefore not innovative.	Thank you for your comment.
24.	15	Specialist organisation	The technology (section 2.4)	Need more information on the effectiveness of 'rinsing' as there is minimal contact time. Would we want to moisten an acute wound when already healing and an appropriate dressing will provide the same environment.	Thank you for your comment. The committee did not consider that there is enough evidence for using Prontosan for acute wounds.
25.	15	Specialist organisation	The technology (section 2.5)	Costs need comparison with water or another antimicrobial solution. There may be an equality depending on formulary selection. Affect on Antimicrobial national strategy	Thank you for your comment. Section 2.5 describes the cost of the technology. The committee carefully considered the comparators and concluded that these should be saline or water.
26.	2	Manufacturer	Clinical evidence (section 3.2)	The IFUs allow for varied use with the EAC report (page 8 supporting documentation) acknowledging the variety of uses of Prontosan and that clinical experts had shared that all were appropriate uses of Prontosan depending on wound condition. Prontosan products have the same active ingredients, the difference comes in the viscosity of the products (Gel X being thicker than gel which is thicker than solution) and that the consistency of the product facilitates contact with the wound bed of the two active ingredients. Recommended use of Prontosan is covered in the clinical context of the company submission (page 274 supporting documentation) in line with the conditioimrpon of the wound. In addition, the company provide training material (supplement 1 and 2 provided with Part 1 of the company submission) providing information on how recommended use of Prontosan is communicated to clinicians locally. In acknowledgement of this being unclear to the committee we have shared two active NHS wound care pathways from Leicester and Doncaster & South Bassetlaw – these examples demonstrate how clinicians adapt the use of Prontosan solution and gel depending on the condition and clinical assessment of the wound. We ask that the committee review the comment “Prontosan is used inconsistently” and explores how the use of the product in studies is representative of the pragmatic approach taken clinically in the NHS of adjusting treatment to	Thank you for your comment. The committee carefully considered this comment and made some amendments to this section. It replaced ‘was used not consistently’ with ‘Prontosan use varied across the studies.’ Also, detail of the studies was added on why they varied, including the use of a single irrigation and using the gel without the solution.

				suit wound condition, this may be considered more relevant and informative to NHS practice as outcomes are highly comparable.	
27.	2	Manufacturer	Clinical evidence (section 3.6)	please refer to comment 3.2 which covers active ingredients, adaptable use and outcomes and amend this section accordingly	Thank you for your comment. Please see NICE's response to comment 26.
28.	1	Healthcare professional	Clinical evidence (section 3.6)	The product/s used doesn't change the necessarily change the clinical outcomes as both show improved granulation tissue, reduced slough and exudate and reduced inflammation across a range of studies.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
29.	6	Healthcare professional	Clinical effectiveness overview (section 4.1)	Prontosan wound cleansing solution was selected for use in the wound cleansing policy at DBTH due to evidence that stated: prophlbetaine-polhexanide solution has a significant higher rate versus normal saline in reducing inflammatory signs in the healing of chronic wounds such as vascular leg ulcer and pressure ulcers, surface tension is recued and removal of debris and bacteria without being cytotoxic wounds progressed towards healing.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
30.	2	Manufacturer	Clinical effectiveness overview (section 4.3)	While we appreciate the various ways Prontosan is used can make drawing conclusion difficult however we would like to highlight that the different products all contain the same active ingredients in the same quantities. The difference comes in viscosity of the product allowing for varied contact times with the wound bed, contact time with all wound care products and dressings varies due to the nature of the individual requirements of each individual wound. National guidance recommends wound condition is assessed every 28 days and wound care adjusted accordingly to the condition of the wound. We request the committee treat the Prontosan products as the same one product when reviewing the clinical impact of the products and review the guidance accordingly.	Thank you for your comment. Section 4.3 has been amended to reflect the discussion and the statement that 'clinical experts agreed that both the solution and gel have the same ingredients and should be considered the same product' has been added.
	Technology – clinical experience				
31.	4	Healthcare professional	Clinical effectiveness overview (section 4.3)	In my practice Prontosan solution and Prontosan wound gel x are used together for all non healing wounds, chronic and acute wounds in need of debridement and all wounds with recurrent infection. The solution is applied as a soak for 10mins.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
32.	8	Healthcare professional	Clinical effectiveness overview (section 4.3)	In community we explain to our staff and patients that the gel continues wound contact with active ingredient of prontosan until next dressing change. Its good to have an option of gel and solution.	Thank you for your comment.

				In our practice using solution solely has an option however we are seeing an enhanced effect with using the solution and gel together. This is definitely an enhanced effect in combination compared to the solution alone. We have now incorporated this into our daily practice.	The committee values comments from clinicians about their experience using the technology.
33.	1	Healthcare professional	NHS considerations overview (section 4.9)	Although many years ago I was part of the formulary group when prontosan was extensively evaluated for our County wide formulary; it would have been the only change made. Dressings and/or compression therapy would have been continued. The results of that change indicated it was worthy of formulary inclusion and has remained so ever since and we have not considered its removal or change to other solutions during that time. Because of the success of Prontosan and the reliability of it, it has been accepted in many places as part of a 'woundcare package' but pathways clearly identify core wound cleansing guidelines. using prontosan as part of a wound care package should not be viewed negatively.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Section 4.10 describes Prontosan being part of a bundle of care and the importance of consistent and appropriate wound care pathways for chronic wounds.
	Technology – wound cleansing				
34.	2	Manufacturer	Clinical effectiveness overview (section 4.3)	There has been much discussion on the “need” to cleanse wounds in the creation of this guidance – we would like to highlight updates to the NATVNS wound cleansing pathway reports that “if the wound is chronic, infected, have debris ore residual dressing in place OR if the patient is at high risk of wound infection then cleanse the wound and consider using a biofilm disrupting cleansing solution”, a “biofilm disrupting cleansing solution” is described in the pathway as one such as PHMB polyhexanide and betaine. http://www.healthcareimprovementscotland.org/our_work/patient_safety/tissue_viability_resources/wound_cleansing_pathway.aspx In addition the updated National Wound Care Strategy Programme lower limb guidance instructs wound cleansing as immediate care and required at each dressing change as required. We request the committee utilise these update guideline in reference to need for cleansing rather than use of expert opinion alone.	Thank you for your comment. The EAC has reviewed the National Association of Tissue Viability Nurse Specialists (Scotland) wound cleansing pathway and the updated National Wound Care Strategy Programme lower limb guidance and noted that the guidelines do say to consider use biofilm disrupting cleansing solutions, for example PHMB polyhexanide and betaine. Section 4.3 has been amended to include the guidelines.
35.	2	Manufacturer	Relevance to the NHS (section 4.7)	We would like to make the committee aware that recent updated national wound care programme recommends for lower limb ulcer that “at every dressing change: cleanse the wound bed” (page 12 of lower-limb recommendations). This is a clear up to date UK guidance. We would like to highlight again regarding update of NATVNS guidance regarding cleansing and how PHMB containing products are named in this guidance. Cleansing of wounds with Prontosan has recently been	Thank you for your comment. Please see NICE’s response to comment 34.

				added (February 2021) to the Scottish wound cleansing pathway “if the wound is chronic, infected, have debris ore residual dressing in place OR if the patient is at high risk of wound infection then cleanse the wound and consider using a biofilm disrupting cleansing solution”, a “biofilm disrupting cleansing solution” is described in the pathway one such as PHMB polyhexanide and betaine. NATVNS guidelines have been submitted for committee review. We as the committee to review all reference to recommendations to cleansing the wound bed and reflect how this may change the committee’s decisions regarding Prontosan.	
36.	2	Manufacturer	NHS considerations overview (section 4.9)	The protocols for the RCTS demonstrate action was taken to limit the variation of secondary dressings, mostly reporting on using simple foams or adherent dressings. Studies always excluded for wounds with a confirmed infected wounds so antimicrobial dressings were not used. There is no evidence from the RCTs that any advanced interactive dressings were used and the studies were designed to investigate the impact of Prontosan vs standard care.. In comparative studies such as Andriessen it is detailed that the VLUs were all receiving full compression therapy therefore this was equal care for both groups. The variation in wound care is a well discussed topic and one which affects all wound care products. The pathways provided from the company as a supportive implementation tool to local NHS areas adopting Prontosan aim to help limit this variation in care which all wound care treatments and products are subject to. This is more of an adoption comment and practices and variations existing within the NHS should not limit the applicability of an easy to use product which is recommended in national guidance. We request that the committee reviews the company pathways and the Leicester and Doncaster local pathways to see how this issue is tackled locally – there are also several write ups from TVNs adopting Prontosan which were excluded from the EAC report due to the low perceived quality of the journals they were published in, we have submitted these for review as: Collier, Grothier, Kilroy-Findley, and ‘Vernon & Moore’	Thank you for your comment. Section 4.9 is now section 4.10 in the guidance document. The EAC reviewed the local wound care pathways and the additional non-peer reviewed evidence. Section 4.10 has been amended to include ‘examples of local wound care pathways where Prontosan had been implemented were provided during consultation.’
37.	8	Healthcare professional	NHS considerations overview (section 4.9)	We have found it very easy to intregrate prontosan into our local wound care pathway. Nobody has had any problems to the product and the improvements we have had are inline with the evidence provided.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.

				Can I just note the the NWCSG have just updated their lower limb workstream which includes recommendations on cleansing at each dressing change, and the importance of reporting regular wound assessments. Which should be used to review patient wound management.	The committee has been made aware of these recommendations from the NWCSG.
38.	2	Manufacturer	Outcome measures (section 4.5)	The clinical experts said Prontosan should be used until wound closed and not just to improve wound healing – This statement was made during the open committee meeting from one expert and the committee should be aware that may reflect a single opinion rather than the general consensus as the EAC report on page 94 in reference to the wound healing model: Clinical experts advised that wound cleansing should only be carried out where clinically indicated, and some experts would not typically use Prontosan products for the duration of healing .	Thank you for your comment. This has been considered and section 4.5 has been amended to reflect clinical opinion.
Improved wound bed condition (n = 23)					
39.	1	Healthcare professional	Recommendations (section 1.1)	Improvements in wound condition i feel has been somewhat lost and that an improved wound bed benefits all wounds and that following to healing would be losing an important clinical outcome that is an improved wound with fewer complications. Evidence of granulation and epithelising tissue is key to identifying progression.	Thank you for your comment. The committee considered improved wound bed condition as an appropriate outcome and section 4.6 has been added to the guidance to reflect this discussion. Please also note that the committee heard in detail from the experts and the ECA that the existing evidence do not support the use of improved wound bed quality as a validated surrogate outcome for complete wound healing. As such it cannot be recommended as the primary outcome to assess clinical and cost-effectiveness.
40.	1	Healthcare professional	Recommendations (section 1.2)	We have to consider here that healing is not always a key marker especially in chronic complex wounds. An improvement to the wound bed quality, clearance and disruption of an insidious biofilm is essential . Clinicians recognise that wound progression is key. Cleansing and thereby improving the wound bed, eradicating biofilm and reducing the bacterial load has a knock on cost saving of being able to step down to core dressings rather than prolonged use of more expensive anti-microbial dressings and/or antibiotic therapy.	Thank you for your comment. Please see NICE's response to comment 39.
41.	2	Manufacturer	Recommendations (section 1)	Within comments to this recommendation we provide reference information on:	Thank you for your comment.

				1) UK National Wound Care Strategy Programme recommend cleansing lower limb ulcers at every dressing change. 2) UK National Wound Care Strategy Programme recommend cleansing diabetic foot ulcers at every dressing change as clinically required. 3) Health Improvement Scotland has recommended cleansing when a wound is chronic, and propose use of a PHMB containing product (such as Prontosan) 4) UK CQUINS highlight importance of wound assessment as a primary outcome measure for healthcare, rather than wound healing. 5) UK National Wound Care Strategy Programme reports wound assessment occurs at a minimum of every 28 days. 6) Wound assessment tools are clinically informative of wound condition and progression. These allow clinical adjustment to patient treatment plan to be made at 28 days intervals, in line with wound condition We would like the committee to reconsider their recommendation. We would like the committee to consider the high level of evidence demonstrating how Prontosan improves wound condition rapidly, in a time line supporting UK practice to assess wounds at 28 day intervals. We would like the committee to consider the role of wound condition improvement as an important outcome for wounds and a progression to wound healing and reflect this in their recommendation. We would like to recommend that the committee consider supporting the use of Prontosan for the improvement of wound condition, in between wound assessment periods (circa 28 days). With the option for clinicians to assess ongoing use of Prontosan at each wound assessment. This would align the recommendation with the evidence and the clinical pathways in the UK. The risk of recommending Prontosan in this manner is minimal and the evidence is supportive of a rapid positive impact to wound condition following Prontosan treatment. This would offer cost savings to the NHS and benefit the patient's quality of life as wound condition has large impacts to the patient.	The EAC has reviewed these documents. The committee considered improved wound bed condition as an appropriate outcome and section 4.6 has been added to the guidance to reflect this discussion. See NICE's response to comment 9.
42.	2	Manufacturer	Recommendations (section 1)	Overall the focus of the guidance has been on wound healing as defined by wound closure, much of the evidence for Prontosan observes wound condition improvements in relation to wound healing progress. 'Wound condition improvements' are outcomes which can benefit all chronic wounds, and not just those capable of achieving complete healing or are fast to complete healing (only 49% of chronic wounds completely heal within 12 months Guest 2020). Improved wound condition facilitates and acts as an indicator of progression in wound healing, the improvements	Thank you for your comment. The committee considered improved wound bed condition as an appropriate outcome and section 4.6 has been added to the guidance to reflect this discussion.

				in wound condition with Prontosan occur quickly (within 2 weeks) in a variety of chronic wound types and therefore have the potential to provide fast outcomes achievable for all chronic wound patients which facilitates faster wound healing, this has cost savings to the NHS and quality of life benefits for the patients. Since the submission of Part 1 new National Guidance has been produced around wound assessment, we believe this answers the queries around BWAT's relevance to NHS clinical practice. In addition we have provided details of the 'wound assessment national minimum data set' and locally adapted wound assessment tools which demonstrate that BWAT covers 100% of the Nationally recommended wound assessment criteria. with wound assessments completed by NHS clinicians as part of basic wound care. National recommendations suggest wound care assessments are completed at a minimum of every 28 days. This is this means that standard wound assessment tools utilised in every day NHS clinical practice are highly comparable to the BWAT tool in the RCT Bellingeri and the 28 day time period from Bellingeri matches the 28 days wound assessment frequency of clinical practice in the UK. We hope this provides the clarity that was lacking on the relevance of wound condition to UK clinical practice, and that in light of the National Guidance, and CQUINs requiring wound assessment, this will bring the guidance for Prontosan in line with current and future NHS clinical needs for wound care . Further information has been included in comments in this document. We ask that the committee make recommendations on wound condition improvement (as included in the scope) – in line with current NHS wound care priorities and to facilitate progression to wound healing.	Section 4.8 has since been amended to reflect the discussion about the relevance of the BWAT score to NHS practice. Please see additional response to comment 39.
43.	2	Manufacturer	Recommendations (section 1) Are the recommendations sound and a suitable basis for guidance to the NHS?	The draft guidance in its current form is restricted in the recommendation of use to complete wound healing as defined by wound closure. This is not suitable basis for guidance to the NHS for reasons below. Currently there are 1,582,000 chronic wounds in the UK, 51% of which do not heal in 12 months (806,820 patients), only 37% of VLUs heal in 12 months and this is further reduced to only 18% of VLUs with a confirmed infection (Guest 2020). Wound condition improvements are vital for wounds to progress to healing, by moving the wound from the inflammatory phase of the healing continuum into the regenerative phases of wound healing: granulation and epithelisation; the reduction in	Thank you for your comment. Please see NICE's responses to comments 39 and 42.

				slough, exudate and biofilm facilitate this and prevent infections and markers of infection. The current National guidance (National Wound Care Strategy Programme (NWCSP) Lower Limb Recommendations and Health Improvement Scotland & NATVNS (Scotland guidance)) make recommendations on wound cleansing and wound assessment. Wound cleansing is recommended as immediate care and care at each dressing change for the NWCSP Lower Limb guidance. Prontosan is referenced by ingredients in the Scottish; NATVNS, wound cleansing guideline. In addition, wound assessment tools, used in the UK, track progression to healing. Recommendations on parameters for wound assessment are wholly covered by the BWAT tool used in the RCT by Bellingeri and the BWAT tool is relevant to the outcome measures reported in the RCT by Valenzuela. In addition, outcomes are supported by many of the single arm observational studies. Wound assessment is included in national guidance to be conducted at a minimum interval of 28 days. Wound assessment is included in 3 CQUINS, 2 of which are active for 20/21 this demonstrates that wound assessment is seen as a key driver for improvement in wound care and therefore supports the role that wound condition improvement plays in all wounds (not just those able to heal). By changing the recommendations to recognise wound condition, this guidance can be relevant to current clinical priorities for healthcare professionals in the UK involved in wound care and provide guidance which is relevant to all the 1,582,000 patients with chronic wounds.	
44.	5	Healthcare professional	Recommendations (section 1) Are the recommendations sound and a suitable basis for guidance to the NHS?	I feel some consideration should be given to the improvement of the wound bed and the healing process. The quality of life issues that even small improvements can make to the patient should not be underestimated. It may be reduced odour less exudate, reduced pain or reduced dressing changes, but they can change that persons life in an extremely positive manner allowing them to feel comfortable to socialise and interact more. It can often mean reduced dressing changes which will reduce the pressures on the nursing services. these factors need to be considered and not just the complete healing rate.	Thank you for your comment. The committee considered improved wound bed condition as an appropriate outcome and section 4.6 has been added to the guidance to reflect this discussion. Please also note additional responses to comments 17, 39 and 42.
45.	6	Healthcare professional	Recommendations (section 1)	The recommendation do not currently reflect the evidence for prontosan and the committee should consider that the evidence is high quality for wound care and informative for clinical practice. The committee needs to	Thank you for your comment. Please see NICE's response to comment 44.

			Has all of the relevant evidence been taken into account?	consider that wound condition is a suitable indicator for wound healing progression.	
46.	7	Healthcare professional	Recommendations (section 1) Has all of the relevant evidence been taken into account?	Yes - but I feel that the evidence around wound improvement should be taken into consideration as strong evidence.	Thank you for your comment. Please see NICE's response to comment 44.
47.	2	Manufacturer	Recommendations (section 1.2)	Please see comment to 1.1. Wound healing is intrinsically linked to wound condition and the outcomes from the evidence for Prontosan are informative of this progression. The EAC reported wound condition as wound healing due the dependency of wound healing on the condition of the wound. 2 large RCTs were submitted reporting on standard wound assessment criteria, used in the UK,(please see comment in Overall the focus of the guidance has been on wound)relating to wound condition improvements (Bellingeri n=289 and Valenzuela n=142). We ask that the committee make recommendations on wound condition improvement (as included in the scope) – in line with current NHS wound care priorities and to facilitate progression to wound healing.	Thank you for your comment. Please see NICE's response to comment 44. Please also note that the committee heard from the experts that they had not used the BWAT score in NHS practice.
48.	2	Manufacturer	Recommendations (section 1.2)	This acknowledges the role of improving wound condition in a chronic and acute wound care but the role and importance of wound condition in helping wound healing and isn't discussed in 1.1 or 1.2 or in the recommendation. We would like to highlight that "Changes to wound bed condition including slough, exudate, granulation and oedema" is one of the outcomes in the scope and request the committee reflect on this in their review of the recommendation. Please also see comments to 4.5 & 4.7.	Thank you for your comment. Please see NICE's response to comment 44.
49.	8	Healthcare professional	Clinical evidence (section 3.7)	All 4 studies are linked because you cant have wound healing for example without wound conditioning improving and wound size decreasing. Therefore these 4 studies that are linked to each other show an improvement against saline, so should be judged as having a relationship to each other.	Thank you for your comment. Please see NICE's response to comment 44.
50.	5	Healthcare professional	Clinical evidence (section 3.7)	The studies presented show a number of areas where the prontasan has had an effect on the wound bed and healing process of the wound. They do all interlink as seen in the Bellingeri study to show an improvement in	Thank you for your comment.

				the wound . looking at the wound healing continuim and the way we assess wounds allows us to see evidence of wound healing or wound health by looking at the individual tissue forms and wound bed tissue type percentiles. It is the monitoring of these different factors that allow the clinician to visualise the improvement of the wound and give physical parameters to show tissue change and wound healing. It is only by linking the changing parameters of the wound size and tissue type that we can show healing and see if the product has a positive effect. Just concentrating on one aspect cannot give the full view of the wound healing process merely an indication of what effect the product may have on the wound.	The committee values comments from clinicians about their experience using the technology. Please see NICE's response to comment 44.
51.	2	Manufacturer	Clinical effectiveness (section 4.1)	Regarding chronic wounds, two large RCTS (Bellingeri and Valenzuela) demonstrate rapid, significant improvements in wound condition in 2-4 weeks in chronic wounds. Wound condition is a requirement for the progression to wound healing and further detail has been supplied on this relevance to clinical practice. One small RCT and the non-randomised comparative study reported faster healing times when wounds were treated with Prontosan compared with saline. These studies support the clinical experts who reported wound condition improvements and wound healing in the open committee discussion. The observational studies report on wound condition improvement and faster healing in line with the RCTs . The single arm studies report on impact of moving from standard care to Prontosan and support the comparative evidences, please reefer back to comments on In section 3.7 for details We would like to highlight recent guidelines change from Scotlan to include PHMB containi products in the wound cleansing pathway an dremnd the committee that the EAC support the case for use of Prontosan in Chronic wounds. We request the committee review this sentence in the	Thank you for your comment. Please see NICE's response to comments 10 and 44.
52.	2	Manufacturer	Clinical effectiveness (section 4.1)	The evidence include two large RCTs (significantly powered as discussed previously and low-some concerns of risk only) which report large improvements in wound condition compared with saline in chronic wounds. We request that the committee review the evidence in line with wound condition being a requirement to achieve wound closure and a clinical indicator of progression of healing. Reviewing the evidence in this manner would align the NICE guidance with recent national guidance updates to the national wound care strategy programme, Scottish wound cleansing guidance (which references Prontosan by ingredients) and with the NHS CQUINS which state importance of	Thank you for your comment. Please see NICE's response to comments 10 and 44.

				wound assessment in the progression to wound healing. Further detail below/ point 4.7	
53.	2	Manufacturer	Side effects and adverse events (section 4.4)	During the open part of the committee meeting the committee members asked what was the role of wound condition in wound closure. We would like to highlight that the company provided referenced background material of the role of wound condition (slough/exudate and biofilm) in wound healing and the role of the presence of slough, excess exudate and biofilm in the "stalling" of wounds in the chronic inflammatory phase (please refer to page 14 paragraph 2 of the company submission). Briefly, the company covered "chronic wounds often occur when there is a delay in progressing through the stages of healing (Dowsett and Newton 2005), typically persisting in the inflammation stage, which can delay wound healing (Halim, Khoo, and Mat Saad 2012). Slough and exudate are produced in response to inflammatory factors present in the wound bed (Parnham and Bousfield 2018; Newton et al. 2017)."……." The effects of slough, excessive exudate and biofilm within a wound contribute to delayed healing, and must be removed to create an ideal environment for a wound healing (Percival and Suleman 2015; Murphy et al. 2020)." We request the committee please consider the importance of wound condition as this explains why faster wound heling is observed in the comparative studies. Would closure is a final objective of caring for the majority of wounds, the importance of tracking progression to wound healing, through wound assessment, has been recognised as key to achieving wound healing and preventing wounds from failing to, or being delayed in, healing. As a result wound assessment was included as a CQUIN for 2017-19 "Indicator 10: improvement of assessment for wounds" stating the rationale for selection as: "Failure to complete a full assessment can result in ineffective treatment and contributes to delays in the rate of wound healing for patients. This has significant consequences for patients in respect of their quality of life as failure to treat wounds correctly can lead to delays in healing or failure to heal." https://www.england.nhs.uk/wp-content/uploads/2017/07/cquin-indicator-specification-information-january-2019.pdf In addition wound assessment continues to be a highlighted requirement in the most recent CQUINs for 20-21, "CCG11: Assessment, diagnosis and treatment of lower leg wounds" and "CCG12: Assessment and documentation of pressure ulcer risk" We advise the committee to be aware that these CQUINS are focused on wound assessment, wound	Thank you for your comment. Please see NICE's response to comment 44.

				healing is not required as an outcome. We ask the committee to consider wound condition improvements, as measured by wound assessment tools, as an outcome relevant to UK current wound care practice. https://www.ahsnnetwork.com/cquins-for-wound-care https://www.england.nhs.uk/wp-content/uploads/2020/01/FINAL-CQUIN-20-21-Indicator-Specifications-190220.pdf (page 29 and 30 report on CCG11 and CCG12) https://www.ahsnnetwork.com/app/uploads/2019/11/V2-Draft-Lower-Limb-Assessment-Essential-Criteria-25.11.19.pdf We would like to make the committee aware that the EAC classed wound condition under the wound healing heading within tables 13 – 16 of their report. 2 large RCTs were submitted reporting on wound assessment criteria relating to wound condition (Bellingeri n=289 and Valenzuela n=142),We ask that the committee make recommendations on wound condition improvement (as included in the scope) – in line with current NHS wound care priorities and to support progression to wound healing.	
54.	1	Healthcare professional	Outcome measures (section 4.5)	Wound healing does not acknowledge wound condition improvements as a viable outcome. it is imperative that non-clinicians accept that wound condition improvements such as increased granulation tissue, reduced pain, decreased slough and exudate etc. are 1) indicative of progression in wound healing (i.e. out of the inflammatory stage of healing) and 2) wound condition applies to all chronic wounds and something all patients would benefit from not just those that are capable of healing (49% of chronic wounds are over 12 months, Guest 2020). Despite multi-disciplinary interventions, excellent care and holistic approaches, some patients will not heal and this is sadly accepted and realistic. However we seek as clinicians to optimise that wound for the patients sake, cost effectiveness and their quality of life. This should never be disregarded as a valid outcome however difficult it is the validate scientifically.	Thank you for your comment. Please see NICE's response to comment 44.
55.	2	Manufacturer	Outcome measures (section 4.5)	This was commentary from the open committee meeting, this was the rationale provided by the expert for why in their clinical practice they chose to use Prontosan preventatively after the improved wound condition was achieved and progression to healing facilitated with Prontosan – this was explained as to prevent any stalling or deterioration	Thank you for your comment. Please see NICE's response to comment 44.

				of wound condition which would delay or cause degeneration of wound healing – this statement does not prevent Prontosan being used to improve wound condition and we ask the committee to consider this in their discussion and review the option that Prontosan does not need to be used in a binary fashion i.e. until closure/healing or to improve wound conditionand that this is reflected in the evidence also. Based on the evidence and in line with UK practice the evidence support use of Prontosan to improve wound condition between wound assessments (4 weeks in the UK according to the updated national wound care strategy programme.), then the clinical can decide if further wound condition improvement is require and continue or stop Prontosan accordingly to the needs of the wound and the patient based on wider co-morbidities. We request the committee review their decision not to support Prontosan and request how Prontosan use aligns with wound assessment guidance and that the evidence support wound condition is re-considered	
56.	2	Manufacturer	Outcome measures (section 4.5)	Leg ulcers which have healed can recur if compression is not continued however, in this healed state there is no wound to dress and the patient will be discharged from thretissue viability nurse and only with 6 monthly check ups with the practice nurse. During this time Prontosan would not be used. Unhealed leg ulcers can deteriorate and there could be scope for use of Prontosan to prevent wound deterioration. Following nation guidance to perform a complete wound assessment every 4 week clinicians can review the wound condition and choose to continue or stop treatment. In line with the wound condition RCTs demonstrating improvement after 2-4 weeks treatment with Prontosan, the committee could include use of Prontosan, in line with national guidance, to be used to improve wound condition and reviewed every 4 weeks. We request the committee consider this option based on the evidence for wound condition and the national guidance to review at 4 weekly intervals.	Thank you for your comment. Please see NICE's response to comment 44.
57.	2	Manufacturer	Outcome measures (section 4.5, 4.9)	Additional evidence following wounds until complete closure would be insightful, however complex, as described above the experts report how wounds can last up to 4 years and Guest 2020 reports that only 49% of wounds heal within 12 months (this would make for a very long study). In addition the committee report in section 4.9 that Prontosan is used as part of a wound care package. Currently in the UK wound care pathways vary across the country which may increase the difficulty/size of an appropriately RCT. Any RCTs standardising care to definitively	Thank you for your comment. Please see NICE's response to comments 10 and 44.

				determine the impact of Prontosan may have strong internal validity (reporting on one Prontosan product alone in conjunction with standardised care pathways) may lack external validity and allow for easy generalisation interpretations By looking at wound healing judged as complete closure the committee are excluding the wounds that are never likely to heal, this potentially excludes patients where a more inclusive recommendation of 'wound condition improvements' could be achieved. Wound condition is progression toward healing, and indeed required to improve before healing can be achieved, and we request the committee reflect on their decision not to support Prontosan considering the more robust evidence supports use of Prontosan for wound healing	
58.	4	Healthcare professional	Outcome measures (section 4.5)	With all chronic wounds there is always going to be a small percentage of patients that take a longer time to heal. In my practice I would say approximately 15% of patients take longer than 1 year to heal.There is also a small percentage that will never heal. In wound healing particulary chronic wounds, a desirable outcome is removing the bacteria burden, improving the wound bed- removing slough and devitalised tissue, reduction in wound size and exudate. As long as a wound is improving whether it be reduction in pain, infection or moving a static ulcer on to the next phase of healing is a positive and realistic outcome.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Please see NICE's response to comment 44.
59.	6	Healthcare professional	Outcome measures (section 4.5)	We would agree with Bellingeri that wounds with reducing devitalised tissue. reducing exudate levels, reducing inflammatory sins and reduced surface area all provide evidence that the wound is progressing though the stages of healing. This is relevant o how clinician assess the progress of a wound. Due to underlying conditions and co mobilities some wound do take several years to heal. It is important to prevention further complications to wound healing by reducing the risk of biofilm formation and infection by cleansing the wound at each dressing change. I would reencourage NCE to make the recommendations on protosan based on improving the conditions of wound bed preparation, such as the with the Bellingeri results. As we have experienced reduced infection rate, increased healing, reduced cost and nursing time and a reduction in the need for advanced dressings enabling patients to self care.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Please see NICE's response to comments 10 and 44.

60.	8	Healthcare professional	Outcome measures (section 4.5)	In clinical practice we were using the product initially to improve the condition of the wound bed. However when reviewing the evidence we re evaluated our practice so that we use prontosan from referral of the wound to clinician to the wound healed as this not only enhances the wound healing but additional maintains good wound bed health. However, using the product for wound bed condition improvement is a viable use of prontosan, which in my experience my patients and clinicians would benefit from guidance on. Wound healing can only occur when the wound bed is in a healthy state for example exudate, slough have been resolved. Wound condition tracked through weekly wound assessments and measuring granulation and slough % etc give us a good indication of the wound progression .	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Please see NICE's response to comment 44.
61.	2	Manufacturer	Outcome measures (section 4.6)	As per comment in 3.10 We ask the committee to review the Bellingeri paper in light of the large improvement in wound condition which occurred in a 4 week period following Prontosan treatment compared with saline, rather than focus on what the score of 14 is in reference to. We ask the committee when considering wound condition to think of the patient, in section 4.12 the committee request more PROMs, however the QoL data supplied has not been considered. Wound condition improvement will improve excessive exudate, smell and pain – these are important patient parameters – this id discussed in detail in the company submission on pages 93 and in the EAC report, 49,57 and 58). We ask the committee review the impact of their recommendations to focus on wound closure and the impact on the patient with improvements to wound condition.	Thank you for your comment. The committee considered this comment carefully and recognised the uncertainties in the reporting of the BWAT score in the Bellingeri 2016 paper. No changes were made to this section. Please see NICE's response to comment 17.
Clinical evidence (n = 82)					
62.	9	Healthcare professional	Has all of the relevant evidence been taken into account?	Yes but not necessarily been given the credit it deserves Pharma RCTS to support use of products should be commended these often don't exist and will never be of the same homogeneity and lack of bias as NIHR HTA studies	Thank you for your comment.
63.	3	Healthcare professional	Has all of the relevant evidence been taken into account?	Yes, I believe it has	Thank you for your comment.
64.	7	Healthcare professional	Has all of the relevant evidence	I do not feel that all of the evidence has been taken into account. There are 35 clinical evidence papers supporting the use of Prontosan which is	Thank you for your comment.

			been taken into account?	far more than any cleansing solution. The evidence is of good quality and includes randomised controlled trials. There is also evidence for its use over normal saline and why it is more beneficial.	Please see NICE's response to comment 10.
65.	15	Specialist organisation	Has all of the relevant evidence been taken into account?	Evidence not current and practice has changed since launch 13 years ago and much of the presented evidence should be discounted.	Thank you for your comment.
66.	2	Manufacturer	Has all of the relevant evidence been taken into account?	We would like to highlight that 'real-world' reports which were presented at wound care specialist congresses and then written up, by clinical specialists and Lead Tissue Viability Nurses, have not been included by the EAC. This was due to the nature of the publications they are reported in, not being peer-reviewed. We believe these offer insights into the 'real world' clinical experience of how Prontosan is used in clinical practice in the UK, and the outcomes and results seen are consistent with the scope and those reported in the RCTs and observational studies. These additional publications are of benefit as they provide insights, and detailed patient quality of life testimonies. These answer some of the clinical relevance queries raised by the committee Below is a summary of information from these UK publications: Kilroy-Findley (Leicester partnership trust LPT) – successful implementation of a biofilm pathway including Prontosan solution and gel using a 'three phase' biofilm pathway, wounds were assessed at 2 weeks and if wound condition had improved treatment was adjusted into the next phase. "The development of the LPT biofilm pathway has provided community nurses with a tool to improve patient quality of life through reducing exudate, odour and — where there are no insurmountable barriers — healing." Two patient testimonials are provided as part of the case studies included. Patient (1) with non-healing leg ulcer: "I was in constant pain, which meant I had to take lots of pain killers – all different types. These made me feel tired all the time and never really took all the pain away. I became less mobile and this effected my walking. I was always getting antibiotics, which also made me feel sick. My legs were constantly wet and leaking and really smelt bad. It was embarrassing. It used to stress me out because I was always having to ring the nurses up, it took ages to get through and when I did see a nurse I felt guilty because I felt like it was my fault, I was holding them up and making them really busy. My dad was getting really worried because it was taking so long. "Since	Thank you for your comment. The EAC has reviewed these real-world reports and noted that given the volume of published evidence available he EAC would not include single case reports/real-world reports such as these. The clinical experts have provided detailed information on how Prontosan is used in practice and looking at the information provided in this comment, there is alignment with what the experts have said and what is being reported in these case reports. For the quality of life comment, please see NICE's response to comment 17.

				starting the biofilm pathway my leg has got better. I have virtually no pain now. I have come off a lot of the pain relief, so I don't feel as tired anymore. I don't need any more antibiotics. I don't feel stressed because I don't need to ring the nurses. I don't get the guilt now. I go to clinic at set times for set periods of time, the nurses know what to do, and the care is consistent. "I like having my own dressings and passport to bring to clinic. I know I've got everything we need. The smell is gone and my leg doesn't leak any more. It's nearly healed. I'm able to go out with my dog now and I'm not embarrassed when I see my friends." Patient (2) with bi-lateral leg ulcers: "I had these ulcers for over 2 years and they wouldn't heal. I had cellulitis two times and ended up in hospital having really strong antibiotics that had to be put into my veins. I then had to have the nurses come to my home to give them to me. The pain was constant – it kept me awake at night. My wife was worried and felt helpless that she could not help me. I stopped going to visit my grandchildren due to the fear of them catching my legs because of the pain. I was also embarrassed of the smell. I remember one Christmas when the family got together, I didn't want to be there. I sat at the back of the room because I was so worried about the smell. I remember wrapping the bandages up with cling film to try and disguise it. I never went again after that. I became socially isolated. "I became frustrated as they [the Trust] would send agency nurses and I was never sure if anyone was going to come. I was constantly ringing up. I felt guilty that I was having to keep having nurses come – I know how busy they are. I was frustrated because the ulcers were not healing, nothing was moving forward. There was no continuity with dressings: one nurse would use one thing and another would use something else. I lost faith in the nurses. "Then the tissue viability nurse came and put this plan into place to start the biofilm pathway. She put my mind at rest. We started the pathway and things started to change. I could see it working. I felt like there was light at the end of the tunnel. The smell soon went. I felt like I was back in control. My right leg has healed really fast. I can put shoes on again because I'm in hosiery. Even wearing trousers again without the bandages sticking. I'm more mobile again. My left leg is nearly healed. "I've learnt a lot about this pathway and I see other people in bandages and feel like I'm one of the lucky ones. It's like a huge weight lifted off my shoulders." Collier – 92% reduction in infection rates (544 infections reported in 2013, level of infection reduced to 42 in 2016) in United Lincolnshire Hospitals NHS Trust following the introduction of the Prontosan solution	

				and gel pathway. Prontosan use was adjusted accordingly to wound condition (Fig. 4) The publication report that results were sustained over 3 years. Vernon & Moore – presented at EWMA 2019, an overview of how the Skin Integrity Team developed and implemented a wound cleansing policy using Prontosan, and the rationale for choosing Prontosan. "The Wounds International 2016 reference material formed the basis for the new Policy as of its sound evidence base. Having reviewed the evidence, the team chose to introduce a wound cleansing solution containing PHMB due to its recognised effectiveness against planktonic and biofilm bacteria. As Prontosan Wound Irrigation Solution can be used as a soak during wound cleansing, a soak time was included in the development of a Wound Cleansing Policy. A two pronged approached was adopted for the policy design which comprised of: • Step 1 - Wound Cleansing Policy • Step 2 - Prontosan Wound Irrigation Solution User Guide The user guide uses a step by step approach for clinicians to follow this has been a key to the success of the new policy." Grothier – Results of a 4 week audit undertaken on 151 patients following a pathway including Prontosan solution "The majority of wounds as assessed by the tissue viability staff showed improved healing progression over the 4-week period". Results on wound condition parameters e.g. exudate, size, presented in table 3.	
67.	10	Healthcare professional	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	I feel they are reasonable as managing any wound especially an infected would can be costly in the effective wound care management so by the early implementation of a PHMB solution (prontosan) in the cleansing and irrigation of a wound This can reduce possible infections, reduce biofilm and reduce barriers in effective wound healing	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
68.	3	Healthcare professional	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	yes	Thank you for your comment.
69.	5	Healthcare professional	Are the summaries of clinical and and	I think the 4 RCT and other evidence is sufficient to allow me to make informed decisions about the effective clinical use of the products.	Thank you for your comment.

			cost effectiveness reasonable interpretations of the evidence?		
70.	7	Healthcare professional	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No - please see my comments below.	Thank you for your comment. Please see comment 71.
71.	7	Healthcare professional	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	I have worked in the NHS for 22 years and have used Prontosan products for over 10 years. The quality of evidence for Prontosan (4 RCTs, observational studies, Moller study with 900+ patients 60% of which were DFUs) supports my use of the products as similar products do not have this evidence base. The mix of chronic mixed wounds (Leg ulcers, pressure ulcers, DFUs) is representative of the mix of chronic wounds seen in community and is representative of the patients I see every day. The amount of evidence available at the moment is more than I would expect and has helped inform my decision on using Prontosan Solution and Gel X. There is very good evidence to support the clinical effectiveness of Prontosan, no more in my opinion is necessary to inform clinical practice. The amount of evidence available for these products is much greater than other products recommended by NICE such as PICO and Debrisoft. The Bellingeri study shows faster wound progression with Prontosan use compared to saline. Improvements in wound condition such as slough reduction and wound size reduction are excellent clinical outcomes for the patient and clinician. Some wounds may be slow to heal due to intrinsic factors so any wounds that show improvement with these products are important so we should not dismiss this evidence. There is no evidence for the use of water/saline in wound care so I don't use this in clinical practice. I always try to use evidence based products such as prontosan and from my clinical outcomes I know it works. Even if the evidence isn't comparative directly to saline, because you are introducing Prontosan into care this is a useful comparator to no cleansing at all eg. Moller was not using Prontosan and the infection rate was 41%, after they switched to Prontosan the infection rate was 3% - still informative even if it's not a blinded RCT. I also feel observational studies are useful in wound care because we are observing the effect of	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.

				the wound care treatment and how it works in clinical practice. Wound healing will not occur unless there is an improvement in the wound bed condition - i.e. reduction of slough/debris and destruction of biofilm which can stall it in the inflammatory phase of healing. The wound should then decrease in size. Saline and water can not remove slough or destruct the biofilm so will not show any progress in wounds that are chronic. I have had excellent outcomes using the Prontosan products. The solution is all we use in our clinical settings due to the evidence base. There are 4 RCTs supporting Prontosan use which have informed my teams use of Prontosan over saline. The Lower Limb guidance from the National Wound Care Strategy recommends cleansing at every dressing change and this is relevant to podiatry wounds.	
72.	7	Healthcare professional	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	When looking at clinical evidence I think that wound improvement including pain, infection and wound bed measurement reduction are all extremely important. It should not just be based on wound healing. There are a number of patients with wounds that have inoperable vascular disease so are unlikely to heal but as a clinican you want to keep them infection free and as comfortable as possible. This is the same for terminal patients with wounds. Some patients may also be awaiting further surgery to aid the wound healing such as reconstructive surgery and the key objective again is to get the wound bed clean and infection free before surgery. Reduction in infection rates is extremely important to clinicians as death from sepsis is extremely high particularly in the diabetic population. The cost model is a reasonable interpretation. From my experience of using the prontosan products I have seen an improvement in wound outcomes including infection and imrproved wound healing which will reflect a reduction in the use of staff time, antibiotics and hospital admissions.	Thank you for your comment. Please see NICE's response to comment 44.
73.	15	Specialist organisation	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	No. Clinical evidence is too variable, with no timed clinical outcomes / PROMs. Should not be compared with water or saline as they are both inactive, compare with equivalent product. Cost model not real life, so flawed and statistic based	Thank you for your comment. The committee carefully considered the comparators and concluded that these should be saline or water.
74.	2	Manufacturer	Are the summaries of clinical and and cost effectiveness reasonable	No. The committee has reviewed and reported on the data with a focus on splitting by wound sub group rather than looking at the "chronic" wound as a whole cohort. UK data (Guest 2020) demonstrates the variety of chronic wounds which healthcare professionals manage in the UK reporting 1.58 million chronic wounds broken down as: Venous Leg	Thank you for your comment. The evidence was presented by wound subgroup, however the committee considered the evidence for chronic

			interpretations of the evidence?	Ulcers (560k wounds, 35% of chronic wounds), Leg Ulcer Unspecified (361k, 23%), Diabetic Foot Ulcers (326k, 21%), Pressure Ulcers (202k, 13%), Leg Ulcers mixed (102k, 6%) and Leg Ulcers arterial (31k, 2%). We would like to highlight that the EAC consulted with experts on the relevance of the evidence in section 8 of the EAC report (pg 71) "Clinical expert input suggests that chronic wound management approaches are likely to be similar regardless of wound aetiology therefore the EAC considers that results from studies including patients with wounds from mixed aetiologies are broadly generalisable while acknowledging some limitations." By the recommendation not interpreting the evidence for all chronic wounds the recommendation is not a reasonable interpretation of the evidence with respect to the nature of wounds in the UK In addition the review of the evidence has a focus on the number and interpreted quality of the studies, with minimal reporting on the outcomes measures as defined in the scope. This is not a reasonable representation of the evidence, as many of the outcome measures have not been reported on within the recommendation e.g. wound condition and its role in wound progression to healing and the impact of the wounds and its condition on patient and their reporting on quality of life. There is a focus within the recommendation on the risk of bias reporting of the study. This appears to be a major focus of the committee and while reference is understandable, considering the EAC and the opening comments in the meeting stated that there was more evidence than expected it feels that the risk of bias and sample size of the studies is overly commanding the committee's thought process. NICE have supported products to improve wound condition with less evidence than supplied here. The committee has mis-represented the risk of bias of the RCTs, highlighting one RCT as low risk of bias and implying all the other RCTs were at high risk, however, only one RCT was deemed at high risk of bias. This is not a reasonable representation of the evidence. The RCT at high risk of bias has been overly highlighted. This RCT represents a single application of Prontosan and would not be clinically relevant to the scope, NHS practice or in line with the IFUs. This RCT is a small study (n=40) and the recommendation currently	wounds together in making their recommendation. Section 4.2 has been amended to reflect this. The guidance has focused on the key studies. The committee had access to the assessment report and assessment report overview and considered the single arm studies in their discussion and recommendation. The committee considered this carefully but no changes have been made to the guidance. Section 3.2 and 4.1 and have been amended in the guidance to reflect the accurate risk of bias assessment for the studies. The committee considered this comment about the high risk of bias being overly highlighted carefully but decided not to change the guidance. The committee considered improved wound bed condition as an appropriate outcome and section 4.6 has been added to the guidance to reflect this discussion.

				disproportionately draws upon information for this study. As protocol does not represent practice in the NHS, this study is not relevant to the NHS and justifiably the committee can choose treat this study as an anomaly in terms of its practical use and exclude the study from analysis. The single arm data, which compares to base line in chronic wounds, supports the comparative studies and should be considered in line with how wounds are assessed against base line in clinical practice in the UK The updated National Wound Care Strategy Programme states, that "accurate wound assessment is essential for monitoring wound healing, as wound size and wound bed status from baseline against which all subsequent treatment effectiveness will be measured". The lack of inclusion of the single arm studies within the recommendation is not a reasonable representation of the evidence. The committee has focussed the clinical evidence and the economic evidence on the wound closure aspect. The company submitted a detailed analysis on how Prontosan has evidence to support rapid improvements in wound condition. Wound condition is required for progression to wound healing, this not appreciated in the current recommendations and is not a reasonable representation of the evidence.	
75.	6	Healthcare professional	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	while wound closure is a definitive end of healing, wound improvements can have a positive effect on reducing recourse and improving patients quality of life e.g. no need for antimicrobials, less dressing changes, no need for advanced treatments). This is relevant for all wound types rather than just those that have potential to achieve full healing.	Thank you for your comment. Please see NICE's response to comment 44.
76.	9	Healthcare professional	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	The BWAT score reflects the components of many UK wound assessment tools and whilst not a UK tool includes the recommended parts of the national minimum data set so is relevant to my practice The evidence does not include healing data but does include improved wound bed state This in my clinical experience usually leads to improved likelihood of healing and therefore the product seems appropriate for this use	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. The committee considered the generalisability of the BWAT score to NHS practice and amended section 4.8 to reflect this.
77.	12	Specialist organisation	Clinical evidence (section 3)	The presented evidence is too weak with too much uncertainty in relation to clinical and cost effectiveness to support widespread adoption	Thank you for your comment.

				of this product across the NHS. This product is not seen as a priority therapeutic intervention for wound care. Background UK wound care is characterised by overuse of interventions supported by limited evidence and underuse of evidence-based interventions. To address this imbalance, it is important that widespread adoption of wound care products for which there is insufficient evidence of clinical and cost effectiveness is not encouraged. Therapeutic interventions for wounds should be evaluated using appropriate methodologies that can reliably detect difference. Questions of clinical effectiveness (such as time to healing) and cost-effectiveness require good quality randomised controlled trials. Different types of wounds (e.g. diabetic foot ulcers, venous leg ulcers) require different types of therapies to address the underlying causes of non-healing. For example, diabetic foot ulcers require debridement, off-loading and often revascularisation while, venous ulcers should be treated with compression. Therefore, studies of adjuvant therapies, such as Prontosan, should be conducted in relevant patient populations where patients are also receiving the relevant evidence-informed therapeutic interventions known to improve healing. Finally, studies evaluating healing should use appropriate outcomes. Wound healing is generally accepted at the primary outcome in wound care studies and for this, complete wound healing (usually 'time to healing') is required as unfortunately (and surprisingly) there is no reliable correlation between 'wound improvement' and healing. Since the care needs of a larger and smaller wound are relatively similar in terms of dressing costs and staff time, reduction of wound size or 'wound improvement' are not valid and reliable surrogate outcome measures. Other relevant secondary outcome measures include pain, and prevention of infection measured by appropriate measures. Review of the presented evidence The evidence presented for Prontosan is as follows: 1. A retrospective study of 112 people (Andriessen et al 2008) This study uses an appropriate primary outcome (time to healing) but the methodology is less robust than an RCT so less likely to produce valid and reliable results, the small sample size is unlikely to be able to detect clinical meaningful and as it is not clear whether the sample included a	Please see NICE's response to comment 10.

				mix of wound types, it is unclear which wound population the results would apply to. 2. An RCT of 44 people (Borges 2018) This study uses an appropriate methodology (RCT) but the small sample size is unlikely to be able to detect clinical meaningful differences. The measured outcomes (wound duration, wound area, necrosis and bacterial load) are relevant to wound care, but do not include the standard primary outcome of time to healing. 3. Randomised controlled trial in 40 people (Romanelli et al 2010) Although this uses an appropriate methodology (RCT) the small sample size is unlikely to be able to detect clinical meaningful differences and it also uses an invalid surrogate as the primary outcome. 4. Pilot randomized double blind study (Harding 2012) Although this uses an appropriate methodology (RCT) the small sample size is unlikely to be able to detect clinical meaningful differences. 5. Retrospective study of 198 children with burns (Ciprandi et al. 2018) The methodology of this study is less robust than an RCT so less likely to produce valid and reliable results. The measured outcomes (adverse events/reactions, infections and interactions/symptoms) are relevant to wound care, but do not include the standard primary outcome of time to healing. More importantly, the study population is children with burns, so any results could not be generalised to the large population of patients with chronic wounds which form the majority of UK wound care 6. Prospective, noncomparative, multicentre study in 56 patients (Kiefer 2018) This is an observational study of people with burn wounds requiring surgical debridement followed by split thickness skin grafts. Therefore, although it uses valid outcome measures the methodology is insufficient for measuring clinical and cost-effectiveness and there is no statistical analysis. 7. Prospective randomized controlled trial in 46 adult patients with partial thickness burn wounds (Wattamploy 2017)	

				Although this uses an appropriate methodology (RCT) the small sample size is unlikely to be able to detect clinical meaningful differences and there is no cost-effectiveness data. 8. Prospective, double blind, randomized, placebo-controlled trial in 40 patients with skin malignancies excised (Saleh 2016) Although this uses an appropriate methodology (RCT) the small sample size is unlikely to be able to detect clinical meaningful differences and there is no cost-effectiveness data. The measured outcomes (bacteria load and signs of infection) are relevant to wound care, but do not include the standard primary outcome of time to healing. 9. Cohort Study in 45 patients (Assadian 2018) This is an observational study in a wide range of wound types. The measured outcomes (bacteria load) are relevant to wound care, but do not include the standard primary outcome of time to healing. 10. Retrospective, multi-centre case series study of 50 patients (Atkin 2020) This is an observational study with a small sample size. The measured outcomes (reduction in wound size) are relevant to wound care, but do not include the standard primary outcome of time to healing. 11. Single-blind RCT in 289 people (Bellingeri et al 2016) Although this uses an appropriate methodology (RCT) it uses an invalid surrogate as the primary outcome. 12. Multicenter observational study in 124 people (Durante et al2014), This is an observational study in a wide range of wound types using invalid surrogate outcome measures 13. Device evaluation in 10 patients in the NHS (Horrocks 2013), This is an even smaller case series using invalid surrogate outcome measures 14. Retrospective data review in 953 patients (Moller 2018) Although this study has a large number of participants, the methodology lacks a comparator and is poorly described.	

				15. Observational study of 70 people (Ricci 2018), This is an observational study with a small sample size on unspecified wound types, short follow-up and using invalid surrogate outcomes. 16. Retrospective case series (patients chart analysis) in 49 patients (Moore 2016) This is an observational study in a range of wound types so incapable of detecting clinical meaningful differences. 17. Open label, noncomparative study in 43 patients (Oropallo et al) Non-comparative and incomplete. 18. Report from the Wounds UK Symposium 2016 (Collier 2016). An observation study in one care provider focusing on reducing infection. 19. Comparative study in 142 people (Valenzuela, 2008) The English abstract for this study (published in Spanish) does not specify the methodology or methods but reports invalid surrogate outcome measures. In conclusion, the presented evidence is insufficient to assess the clinical and cost-effectiveness of Prontosan for widespread use on wounds. As Prontosan is more expensive than standard care (sterile saline/water or tap water) it is unlikely to be cost-effective unless it is clinically effective in promoting healing. This casts doubt on the company's claims that using Prontosan will lead to cost savings of around £[redacted] per patient due to quicker time to healing and less frequent nurse visits. However, lack of evidence of effectiveness is not the same as evidence of effectiveness. There may be certain clinical situations where, despite a lack of evidence of effectiveness, the risks of negative outcomes (e.g., high risk of infection in burns) are judged to outweigh the increased costs of using Prontosan. Therefore, Prontosan should continue to be available for such situations. In brief, the current evidence does not support widespread adoption of this product across the NHS for all types of wound care.	

				de that the presented evidence suggests a possibly useful therapy which requires further research. A proposal could be made to the NIHR for consideration of this topic as a research priority.	
78.	1	Healthcare professional	Clinical evidence (section 3.2)	The diverse nature of the studies mean that some look a wound healing, some at wound size and some at wound condition. this may mean that outcomes were looked at narrowly but they all share a relationship with one another and all encompass progress to healing and have a positive impact on clinical and patient outcomes. The solution and gel have been discussed at length and the competent clinician is very clear how and when to use–the company pathways and application guides are comprehensive for this. The solution and/or gel are the same active ingredients and used to achieve the optimum results. I am certainly able to draw conclusions relevant to clinical practice on how effectively Prontosan works using the studies identified. Sample sizes – I believe the comparative RCT numbers were high and met enough validity size. Other study evidence (which may be of a lower quality) should not exclude the bulk of the positive results. Regarding consistency of soak times-this has to be the decision of the attending clinician and therefore it cant be relevant as an evidenced based outcomes. Different wounds require an adaptive approach. Outcomes i felt were clearly defined in the EAC report as in 'Wound Healing, Wound infection and associated factors, Pain, Dressing' the studies clearly stated they were according to need and/or local protocols which is correct.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
79.	2	Manufacturer	Committee discussion (section 4)	In the committee open meeting Dr Karen McCutcheon presenting the clinical evidence said “there is a considerably healthy amount of evidence, more healthy than would have been expected” the EAC also reported in section 8 there to be a “considerable volume of evidence” (pg 70). The EAC included 7 RCTs, 2 observational studies and 9 non-comparative studies. The outcomes from the scope are supported by a mix of RCTs, comparator and non-comparator studies: 10 studies cover wound bed condition (3 RCTs), 9 studies cover wound healing (2 RCTs), 10 cover wound infection/markers of infection (1 RCTS), 8 studies cover pain reduction (1 RCT), 3 studies cover QoL and 4 studies are direct comparators to saline of which 3 are RCTS. To describe there being a lack of clinical benefit when significant improvements are reported in	Thank you for your comment. Please see NICE’s response to comment 10.

				multiple outcome measures required for the scope (also discussed in section 3.7)	
80.	15	Specialist organisation	Clinical evidence (section 3)	Evidence poor quality with a high risk of bias. Not representing current practice. Consider comparison with other AM solution. Are they suggesting use on all patients rather than water ? Leading cost and AMS risks. Evidence does not show healing rates against standard practice.	Thank you for your comment.
81.	15	Specialist organisation	Clinical evidence (section 3.6)	Agreed	Thank you for your comment.
82.	15	Specialist organisation	Clinical evidence (section 3.8)	Agree with correct patient choice. A local protocol would need to be in place.	Thank you for your comment.
	Clinical evidence – acute wounds				
83.	10	Healthcare professional	Have we considered all of the evidence for Prontosan in acute wounds?	As a Tissue Viability Nurse Specialist I promote the use of prontosan in both acute and chronic wounds. I am in the process of embedding prontosan as first line with wound irrigation across my local NHS provider to assist in preventing and reducing Surgical site infections, reducing wound infections and braking down the biofilm. There a continuous trials ,cash studies being undertaken and I have been fortunate to participate in the with positive results	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
84.	9	Healthcare professional	Have we considered all of the evidence for Prontosan in acute wounds?	There isn't as much in this area Given most wounds are chronic Guest 2020 then the focus should be on chronic in my view	Thank you for your comment.
85.	7	Healthcare professional	Have we considered all of the evidence for Prontosan in acute wounds?	yes	Thank you for your comment.
86.	7	Healthcare professional	Have we considered all of the evidence for Prontosan in acute wounds?	The Moller study has over 900 patients and many of these are diabetic foot ulcers. The evidence is a mixture of chronic wounds which is representative of the type of wounds currently seen in the community setting. The Moller study also saw a large reduction in infection rate when using prontosan solution. This evidence is still informative even though it is not a blinded RCT because it has high patient numbers. I do also think that the evidence from observational studies should be taken	Thank you for your comment.

				into account as this type of data can give more detailed depth of the data collected.	
87.	3	Healthcare professional	Have we considered all of the evidence for Prontosan in acute wounds?	I am unsure	Thank you for your comment.
88.	15	Specialist organisation	Have we considered all of the evidence for Prontosan in acute wounds?	Consider there to be little value in the use of Prontosan in Acute Wounds. Too little evidence to make an informed decision.	Thank you for your comment.
89.	6	Healthcare professional	Clinical effectiveness (section 4.2)	think the focus needs to move away from acute wouinds as a whole and consider the acute wounds that have a high risk of being chronic if they are not mabaged with a preventive plan from the start e.g. diabetic foot ulcers at increased risk of infection would require prevention of infection with the aim of stopping them becoming chronic and experiencing complications. The cost effectiveness of haling acute wounds and preventing them becoming chronic would be see significant cost saving when companied to managing a chronic wound. DBTH use do not specify a wound type as we have used it on all wound types will positive outcomes. In our complex wound clinic we review all types of wounds including pressure ulcer, leg ulcer, diabetic foot ulcer, amputation sites, haematomas, trauma wounds, burns, bites, skin grafts, surgical incisions, dehisced surgical sites.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Prontosan is not supported for use in acute wounds because the evidence is very limited, but the committee recognised that some acute wounds could become chronic.
	Clinical evidence - applicability to NHS				
90.	2	Manufacturer	Clinical evidence (section 3.2)	Please see previous comments within this section (3.2) regarding clinical assessments and adjustments to treatment plans. We would like to draw attention to the EAC report conclusion that the data is generalisable to the UK; on page 71 “the EAC considered that the results would be generalisable to the UK setting as in all cases the population, settings and wound types and the approach to wound management are in line with how clinical experts have described UK practice” . The EAC summary (page 8 supporting documentation) also acknowledge that clinical experts had shared that all uses of Prontosan were appropriate depending on wound condition. The EAC and clinical experts state that the evidence is applicable to the NHS, can we ask that	Thank you for your comment. The committee considered this comment carefully and decided to amend section 3.2 slightly to add clarification around the varied use of Prontosan such as the single irrigation and the use of the gel alone.

				this wording is reviewed. We request committee remove this as the studies are reflective of NHS practice.	
91.	2	Manufacturer	Clinical evidence (section 3.2)	Two studies, included by the EAC were excluded by the company (Assadian 2018 and Borges 2018). These two studies used Prontosan solution for a single irrigation on chronic wounds. The company would agree that a single application is not in line with the IFU as "Application should be conducted frequently in order to achieve and maintain an visually clean wound" We request the committee reviewed the relevance (or lack thereof) of these studies in line with the scope – these studies do not report on wound healing, condition or closure. Neither of these studies provide any follow up – and their clinical relevance has been discussed by the EAC and the company and experts would not expect to see a clinical impact to chronic wound following a single irrigation We ask the committee to weigh the value of these studies with patient n=90 combined, with regards to the clinical relevance to the scope and remove the sentence "it was not always used in a way that reflect NHS practice" as all the remaining evidence covers n=2232 patients treated with Prontosan in a manner consistent with NHS practice i.e. over many dressing changes with the wound condition improving with Prontosan use.	Thank you for your comment. The committee considered this comment carefully but decided not to change the guidance. The limited applicability has been noted in section 3.2 and 3.3.
92.	2	Manufacturer	Outcome measures (section 4.7)	For wounds with the presence of slough the company recommends that wounds are soaked with Prontosan. The RCT by Bellingeri have followed this IFU by soaking the wound. To exclude the confounding factor of the wound being soaked the researchers also soaked the saline group. This allows for internal validity of the study enabling any impact of soaking to be accounted. The EAC found this paper applicable to the NHS setting in table 9. As per 4.5 we have provided additional information comparing the BWAT score parameters to National Guidance and local wound assessment tools – BWAT fulfils all of the required parameters and reflects wound assessment tool parameters – this is highly relevant to the UK. We request the committee reassess how generalizable this paper is to the NHS setting in light of the updated guidance, CQUINS (refer to comments in 4.5 for more details) and every day practice relating to 28 day wound assessments performed clinically.	Thank you for your comment. This section (now section 4.8) has since been amended to reflect the generalisability of the BWAT score to NHS practice.
93.	5	Healthcare professional	Outcome measures (section 4.7)	It is not the general practise to soak wounds within the UK unless you are trying to remove or loosen adhered debris from the wound bed. This is because it has not been seen to have any positive clinical or practical effect on wound healing. It is also not practical in the community setting	Thank you for your comment.

				as it would add an extra 10 minutes to each area episode It may have a detrimental effect as it may through the convection effect lower the temperate of the wound bed effectively stalling wound healing until the temperate returns to normal. The study I understand has to follow the same regimes with the base fluid and the Prontosan.	The committee values comments from clinicians about their experience using the technology. Please see NICE's response to comment 92.
94.	2	Manufacturer	Relevance to the NHS (section 4.7)	While all wounds may not be soaked with saline, we would query whether the impact of soaking with an inert agent such as saline vs irrigating would be expected to be different from one another. Can we ask that the committee review the reason to believe that the results of soaking have a negative impact on the wound. This is an inappropriate route for enquiry when the study is robust and including irrigation with saline compared to a soak with Prontosan would reduce the internal validity of the study. We request the committee reassess how generalizable this paper is to the NHS setting.	Thank you for your comment. Please see NICE's response to comment 92.
95.	1	Healthcare professional	Relevance to the NHS (section 4.7)	I believe the irrigating then soaking with Prontosan/saline was part of the protocol for that RCT. A 10 minute soak should be the default reference point for the soak time with the clinician being able to increase or decrease this as required and indicated. The NWCSP (2020) recommends wound cleansing at every dressing change and this is undertaken almost always within the NHS. Adequate teaching will support the clinician in this. It would be wrong for the company to be too prescriptive in the timings but their 'clock dial' soak applications guides are very much liked by the nursing staff.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Please see NICE's response to comment 92.
	Clinical evidence – BWAT				
96.	2	Manufacturer	Cost evidence (section 3.10)	We would like to address the concerns over the BWAT score. Bellingeri reported a significant reduction in Total BWAT and inflammatory BWAT, the scoring of BWAT to 13-65 represents 65 being wounds in a state of poor condition, 'degeneration', with 13 being wounds in a good condition, 'regeneration' it is important to note that this is a sliding scale with improvements observed by a decrease in score. On the comments from the committee meeting and in this guidance we have extrapolated the wound condition model to 8, the impact of Prontosan is in fact greater, as if the linear regression is extended to BWAT = 8 then it would take an estimate of 42.4 days to reach a BWAT of 8 in the Prontosan group and 117.1 days in the saline group. (Please see additional calculation by the company) It could be argued an exponential fit would be more appropriate if looking to map until the equivalent of a BWAT 8. When an exponential fit	Thank you for your comment. The committee carefully considered this comment but decided to not change the guidance because the uncertainties in the reporting of the BWAT score were not resolved.

				is used, the saline group would read a BWAT of 8 on day 56.1, compared with day 170.1 for the saline group. (Please see additional calculation by the company) Use of the BWAT score supports the RCT and the comparative studies, demonstrating an estimated faster healing rate, more information from the company has been provided on the relevance of tracking healing progress with wound assessment tools. Together with the RCT and the comparative study all three studies support use of Prontosan for faster wound healing. We would also like to highlight new national wound care strategy guidelines for lower limb recommends wound condition is assessed every 4 weeks (28 days) and improvements in wound condition is expected within that time. It would be unusual for a chronic wound to heal in 28 days.	
97.	11	Healthcare professional	Outcome measures (section 4.5)	BWAT score provides a robust method of scoring wounds and would be something I would use in clinical practice	Thank you for your comment. The committee considered the generalisability of the BWAT score to NHS practice and amended section 4.8 to reflect this.
98.	11	Healthcare professional	Outcome measures (section 4.5)	despite this being a European tool it is a very robust tool that looks at wound assessments and is something i would use in clinical practice	Thank you for your comment. Please see NICE's response to comment 97.
99.	1	Healthcare professional	Outcome measures (section 4.6)	Although this was a tool I was not familar with I have now had a chance to look at it. It is comprehensive, detailed and wholly relevent. My only comment is not about validity but the value of this tool being used in General Practice for example when the average appt time for wound care is only 10-20 minutes. it may be unrealistic in practice. The 13 parameters are relevant and the scoring system within it comprehensive, understandable and revealing as a descriptor. I think the higher reducing score of the prontosan group was compelling compared to the normal saline group. 28 days is a relatively short period of time for a chronic wound study, but the fact that significant (and relevant) reductions in score were shown with the 28 days is even more encouraging.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Please see NICE's response to comment 97.
100	6	Healthcare professional	Outcome measures (section 4.6)	The BWAT tool represents the TIMES wound bed preparation approach we use to assess and document wounds which provide a tracking system to identify if a wound is healing or deteriorating. We would agree	Thank you for your comment.

				with Bellingeri that wounds with reducing devitalised tissue. reducing exudate levels, reducing inflammatory sins and reduced surface area all provide evidence that the wound is progressing though the stages of healing. This is relevant o how clinician assess the progress of a wound.	Please see NICE's response to comment 97.
101	4	Healthcare professional	Outcome measures (section 4.6)	The BWAT assessment tool is representative to all wound assessment tools in that they use prompts to document wound characteristics e.g changes in wound bed, size of wound, exudate type and levels etc This tool gives clear data to confirm a wounds progress and enables the clincian to treat accordingly.	Thank you for your comment. Please see NICE's response to comment 97.
102	5	Healthcare professional	Outcome measures (section 4.6)	The BWAT score whilst not as comprehensive or intuitive as the British and European developed wound assessment tools, it does give enough pertinent information and the scoring system does give easy indication of an improving or healing wound. It does allow the tracking of the wound healing continuum, whilst considering the peri wound area although only up to 4cm from the wound The tool, as used in the study did allow the wound improvement to be seen despite its limitation necessitated by its design for statistical analysis.	Thank you for your comment. Please see NICE's response to comment 97.
103	8	Healthcare professional	Outcome measures (section 4.6)	BWAT - i have looked at this it is a wound assessment tool which includes a comprehensive set of measures that can be used to show wound healing. It covers parameters that we use in our local wound assessment tools. Given that BWAT has a score associated with it which if the score decreases in my clinical experience would should a wound progressing to healing.	Thank you for your comment. Please see NICE's response to comment 97.
	Clinical evidence – Bellingeri paper				
104	2	Manufacturer	Clinical evidence (section 3.2)	The large RCT queried on sample size, Bellingeri (n=289), the methodology stated that for 90% power and 95% confidence, 320 Patients would be required, due to drop out of the study, after recruitment of 320 only 289 were included. Using the data provided in the study for a power of 80% power 95% confidence, the study require need 123 in each arm to prevent type I error with 95% confidence and 80% power to prevent type II error. This study achieved enough participants to achieve an 80% power and 95% confidence, it is inaccurate to report this repeatedly as being under powered. In addition a large effect size with high level of significance was observed in the study. Please remove reference to "underpowered" regarding the Bellingeri paper as this is not accurate from the guidance document	Thank you for your comment. The committee considered that the study is underpowered based on the paper's a priori statistical analysis plan, and this has been added to section 4.7 to provide clarification. Please also note that using the observed effect to perform post-hoc sample size calculations is considered methodologically flawed and it is widely discouraged by experts in statistics as in most cases will lead to dramatic overestimates of power. For more

					information on this please see references below: • http://www.stat.columbia.edu/~gelman/research/published/power_surgery_3.pdf • https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8211362/ • https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6738696/ • https://pubmed.ncbi.nlm.nih.gov/18416448/
105	2	Manufacturer	Clinical evidence (section 3.6)	We have covered the power of the study in comment for section 3.2 and request reference to the power of this study is removed from the guidance.	Thank you for your comment. Please see NICE's response to comment 104.
106	2	Manufacturer	Outcome measures (section 4.6)	For a 0.9 power, Bellingeri et al. stated they required a sample size of 165 patients per arm (alpha of 0.05/ beta of 0.1). From this an effect size of 0.359 can be calculated. Using this effect size, 124 patients per arm are required to achieve a power of 0.8 (alpha of 0.05/beta of 0.2). As such, this study was powered to a minimum of 0.8 using the recruited number of participants (143 in the PP arm and 146 in the NS arm). We ask that reference to this paper being under powered is removed from the guidance and does not impact the committee's review of the evidence.	Thank you for your comment. Please see NICE's response to comment 104.
	Clinical evidence - comparators				
107	2	Manufacturer	Clinical evidence (section 3.1)	Ringers solution – we ask that the committee consider 'saline' and 'saline & ringers' and 'sterile water' to be grouped as one comparator in presenting these results – further detail on the equivalence in comment to 3.3	Thank you for your comment. The committee considered this comment carefully but decided not to change the guidance. The comparators have been presented in the way they were reported in the evidence.
108	1	Health care professions	Clinical evidence (section 3.1)	In my experience 18 studies is a lot more than most wound care companies portfolios I have seen in the past and cited as their evidence. 792 people used in 1 study in my opinion is an excellent representation and cohort in context of an average sized chronic wound care service who would be seen in a month. Definitely representative and enough patients to judge the effectiveness of Prontosan.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.

				I understand that saline and Ringers are comparable to each other – with both functioning as isotonic solutions for cleansing and that results with both of them may be very similar (however i have never used Ringers before so just commenting on its constitution)– but as a clinician regarding saline I am convinced it has no active effect and assume the same for Ringers	Please see additional response to comment 5.
109	2	Manufacturer	Clinical evidence (section 3.3)	The Ringers solution in the product described, Hydroclean Plus, is marketed to 'facilitate autolysis' – there is no active cleansing effect claimed by the company thereby supporting that this is a neutral rinsing agent with no active effect; no evidence is provided to support an active cleansing action of Ringers solution - we ask that this is removed as it is of limited relevance. https://www.hartmann.info/en-gb/brands/l/gb/for-wound-management/hydroclean-plus	Thank you for your comment. This has now been removed from section 3.3.
110	2	Manufacturer	Clinical evidence (section 3.3)	The authors of Andriessen describe that "typically, neutral physiological solutions are used for wound cleansing" both saline and Ringers are inactive isotonic solutions and neutral physiological solutions and can be treated as equivalent neutral comparators to Prontosan having highly similar outcomes: Ringer's solution is defined as: a solution of several salts dissolved in water for the purpose of creating an isotonic solution relative to the body fluids. Ringer's solution typically contains sodium chloride, potassium chloride, calcium chloride and sodium bicarbonate, with the last used to balance the pH. Saline is defined as: a mixture of sodium chloride in water and has a number of uses in medicine, solution is referred to as physiological saline or isotonic saline (because it is approximately isotonic to blood serum, which makes it a physiologically normal solution).	Thank you for your comment. Please see NICE's response to comments 108 and 109.
	Clinical evidence – non comparative evidence				
111	2	Manufacturer	Clinical evidence (section 3.1)	As this section covers all the studies please add the patient numbers from the observational studies for context suggest: "The observational studies cover 1,425 patients in total. The 1,177 chronic wounds moved from standard care (no active cleanser) on to a Prontosan wound cleansing pathway". These single arm studies offer insight into impact of moving chronic complex wounds onto Prontosan from an inactive product (saline/water/ringers) and support the evidence from the RCTs	Thank you for your comment. The participant numbers in section 3.1 are based on the key studies (comparative studies). The committee considered this comment carefully but decided not to change the guidance.
112	2	Manufacturer	Clinical evidence (section 3.7)	Observational data was included and assessed by the EAC which has not been acknowledged here. It should be noted that observational studies, without a comparator arm were tracking the introduction of Prontosan on chronic wounds from baseline treatment of saline or no	Previously submitted The observational studies were included and considered in this evaluation. The

				cleansing. Tracking from baseline is reported as important in the recent National Wound Care Strategy Programme to determine effectiveness of treatment. By omitting the single arm studies, which complement the comparative studies, the impact of change relevant to NHS practice has not been explored - improving wound condition to facilitate wound healing when moving away from standard care (water, saline, or no irrigation) to treatment with Prontosan in addition to the results reported in the RCTs to support the evidence base and link to NHS practice. We request the committee consider how the large body of single arm evidence, comparing to baseline, supports use of Prontosan over standard current care of saline, water or other inert solutions. By reporting on "saline alone", and only reporting on RCTs, the committee have limited the evidence to exclude the larger comparative piece with statistically significant results of faster wound healing with Prontosan compared to saline (Andriessen 2008) where neutral rinsing solutions ringers/saline were used as a control, further details were provided in comments in response to section 3.3 We ask that the committee include the comparative study Andriessen and explore the relationship to the RCT evidence, as well as considering the 'real world observational' studies which were included in the reports by the company and the EAC as this is highly informative to clinical practice.	assessment overview report and medical technologies consultation document present the most critical evidence but all observational studies were made available to the committee in the assessment report.
	Clinical evidence – outcomes				
113	2	Manufacturer	Clinical evidence (section 3.2)	We are unsure what to address here but do note that during the open committee meeting Bellingeri and BWAT score was discussed and its relevance to NHS practice. In order to assist with some clarity we have provided further information on slides which demonstrates how the BWAT score is reflective of data in the Valenzuela study and also applicable to the NHS by comparing with UK assessment tools from National NHS guidance and local wound care formularies. The company submission covers the details of how wound condition can indicate and facilitate wound healing progression (section 2 describe the technology pg 268-9 and section 8. summary and interpretation of clinical evidence pg 348-351). We request the committee review on the relevance of this sentence in light of the additional material supplied highlighting relevance of BWAT to NHS wound assessments and amend accordingly. Similar outcomes may have been reported in such a manner to prevent pooling and direct comparison however both the EAC report (page 49-59	Thank you for your comment. Please see NICE's response to comments 42, 47 and 92.

				in the including tables 13-16) and the company submission (pages 339-357 supporting documentation) drew outcomes together and provided detailed qualitative responses by each outcome and the direction of response was consistent if the effect size could not be defined. We request the committee reflect on how the outcomes measures are representative of meaningful data collected by healthcare professionals in the healthcare setting in the area of chronic wounds	
114	2	Manufacturer	Clinical evidence (section 3.3)	Reported outcomes in VLUs was: rate of wound healing, time to wound healing, wound size reduction, wound infection, pain and wound condition. Please amend.	Thank you for your comment. This is now section 3.4 and has been amended to include rate of wound healing, time to wound healing, wound size, wound infection and factors associated with wound infection (bacterial burden and number of microorganisms) and pain.
115	2	Manufacturer	Clinical evidence (section 3.6)	We request the addition of wound condition to outcomes as requested by the scope	Thank you for your comment. This section has now been amended and references Valenzuela 2008.
116	2	Manufacturer	Clinical evidence (section 3.7)	Pain was reported in a scale in these studies, and binary in Valenzuela as % of patients reporting pain start and end, with a significant reduction in pain observed after 2 weeks in Prontosan group for Valenzuela as well. Please change to include significant reduction in number of patient reporting pain in the Valenzuela paper after 2 week.	Thank you for your comment. This section has now been amended and references Valenzuela 2008.
117	5	Healthcare professional	Outcome measures (section 4.5)	Complete wound healing is always the preferred outcome. However we have a small percentage of wounds that do not heal within a 12 month period and some that take considerably longer. The causes are often multifactorial clinical ,pharmaceutical or social so the improvement in the wounds will often fallout of the timescale/remit of the studies. They do not show the improved quality of life, by making the wound easier to live with, or the extremely slow progression that some of these wound have to get to the healing point when healing had not been presented as an option. I think it is also difficult to measure it against normal saline as abase for effectiveness when we have used sterile water or tap water for wound cleansing for over a decade, as it was previously shown to be of no clinical benefit at the concentrations we use it.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. The committee considered improved wound bed condition as an appropriate outcome and section 4.6 has been added to the guidance to reflect this discussion.

118	15	Specialist organisation	Clinical evidence (section 3.2)	Agreed that outcomes not always clearly reported.	Thank you for your comment.
	Clinical evidence – quality of studies				
119	2	Manufacturer	Clinical evidence (section 3.2)	To refer to all studies as high risk of bias is not correct, please refer to further detailed comments within this section, 3.2 for specific details. In addition the EAC report on page 7 summarises that "despite weaknesses in the evidence (clinical and economic) the EAC considers that based on the current available evidence the use of Prontosan products as an option for chronic wound management is supported" We ask that the title of this section be amended to reflect the true reporting on the evidence	Thank you for your comment. This section and title have been amended to note that only 1 study was at low risk of bias, while 5 randomised controlled trials had some concerns. The rest of the studies were at high risk of bias. Please also note that although the EAC's assessment report is part of the information the committee will consider to reach a decision, the committee's final decision is independent.
120	2	Manufacturer	Cost modelling overview (section 4.10)	The quality of the studies have been addressed in previous comments. Please refer to our previous comments on why the quality of the RCTs for all models was not at 'high risk of bias' or low quality. This has been discussed in earlier comments.	Thank you for your comment. This is now section 4.11, and this has been amended.
	Clinical evidence – sample size				
121	2	Manufacturer	Clinical evidence (section 3.2)	This is not an accurate representation of the 18 studies reviewed by the EAC – 8 studies had less than 50 participants (median 41.5 per study), 4 studies had 50-100 participants (median 61.5 participants), the remaining 6 studies had over 100 participants with the largest retrospective study including 953 participants. We request that the committee reviews the comment that "most of the included studies had small sample size"	Thank you for your comment. The committee considered 50-100 participants to be a small sample size. However, the EAC noted that the sample sizes might reflect the size of the population, and larger sample sizes might not be achievable. This has been added to section 3.2.
122	2	Manufacturer	Clinical evidence (section 3.3)	While the sample size in the RCTs for venous leg ulcers are 34-40 the results of the UK pilot are consistent with the larger non-randomised comparative study in leg ulcers n=112 (Andriessen 2008) we request size of the non-randomised study is added and reporting of wound healing and wound infection in this group and the UK RCT should be mentioned for context.	Thank you for your comment. The committee considered this comment carefully but decided not to change the guidance.
123	2	Manufacturer	Further research (section 4.12)	The evidence submitted by the company covered 1,425 patients, of which 1,177 were patients with a chronic wound. The largest study submitted contained 953 patients in a retrospective data review of real world evidence (Möller 2008). The EAC concluded that while the study	Thank you for your comment. The guidance has focused on the key studies. The committee had access to the

				was “not based in the UK, the treatment protocol for the included patients appear relevant.”	assessment report and assessment report overview and considered the single arm studies in their discussion and recommendation. The committee considered this carefully but no changes have been made to the guidance.
	Clinical evidence – chronic wound types				
124	2	Manufacturer	Clinical evidence (section 3)	The committee report on the subgroup break down results (VLU, burns, surgical sites etc.), there is no summary overall for the group “chronic wounds” as a whole. The company submitted the data overall for chronic wounds (pages 340-355 of the company submission) any by wound sub type (pages 101-103), the EAC only report on wound subtype. As the evidence is representative of how Prontosan is used in standard practice; on a variety of chronic wound types. To only report by subtype is not representative of the outcomes for Prontosan. The EAC summarise in section 8 page 70 of the supplemental material that “based on current available evidence the use of Prontosan for CHRONIC wounds is supported”. We request the committee review the evidence for chronic wounds as a whole cohort for wound condition, reviewing wound condition as progression to healing, this will bring the guidance in line with comments.	Thank you for your comment. The evidence was presented by wound subgroup, however the committee considered the evidence for chronic wounds together in making their recommendation.
125	15	Specialist organisation	Clinical evidence (section 3.3)	As Ringers solution not used in the Community, comparison / results not clear.	Thank you for your comment.
126	15	Specialist organisation	Clinical evidence (section 3.3)	Not relevant to community practice	Thank you for your comment.
127	2	Manufacturer	Clinical evidence (section 3.3)	We would like to highlight that 48% of the wounds in Bellingeri RCT were also VLUs and request the committee consider this study relevant in the context of VLUs as the majority of wound were VLUs and experts commented that these were informative	Thank you for your comment. The committee considered this comment carefully but decided not to change the guidance because the results were not presented by wound type. The study has been included in section 3.3 which covers the different types of chronic wounds.
128	15	Specialist organisation	Clinical evidence (section 3.4)	Acute Trust led issue.	Thank you for your comment.
129	2	Manufacturer	Clinical evidence (section 3.5)	We query why the committee do not discuss all chronic wound data together and request this section is moved to section 3.4 after VLU	Thank you for your comment.

				which are also chronic wounds before changing topic to acute wounds (burns and surgical site) for easy of reading	Section 3.6 has now been moved. In the guidance this is now section 3.3 and it describes the chronic wound types together (section 3.3 and 3.4).
130	15	Specialist organisation	Clinical evidence (section 3.5)	Evidence not clear, of poor quality	Thank you for your comment.
131	2	Manufacturer	Clinical evidence (section 3.6)	While a number of studies reported on variety of chronic wounds within the study, we would request that this section looks at chronic wounds as a whole cohort as the evidence for the single wound studies (VLUs) complements the topic of chronic wounds in general, as VLUs were included in studies containing a variety of wounds. Inclusion of all chronic wound data here would offer a more generalisable insight into the impact of Prontosan. We request the VLU papers from section 3.4 are also included here.	Thank you for your comment. Please see NICE's response to comment 124.
132	2	Manufacturer	Clinical evidence (section 3.7)	The EAC also say "Overall, the results from the studies suggest that the use of Prontosan as a cleansing solution may have some positive impact on wound healing and management, particularly in chronic wounds although the extent of the benefit of using Prontosan versus saline cannot be determined with any certainty based on current evidence." and "the EAC considers that based on the current available evidence the use of Prontosan products as an option for chronic wound management is supported". "We ask that Prontosan as an option for improving wound condition for chronic wound management is addressed by the committee in line with the EAC recommendations and with consideration to the information supplied on wound assessment's relevance to wound condition as progression to healing.	Thank you for your comment. The committee considered improved wound bed condition as an appropriate outcome and section 4.6 has been added to the guidance to reflect this discussion.
133	2	Manufacturer	Clinical effectiveness (section 4.2)	Section 3.6 describes how 10 studies cover different types of chronic wounds, including 2 RCTs (Bellingeri 2016: Valenzuela 2008). Both of these studies cover various chronic wounds (VLU and PU in Bellingeri, unspecified chronic wounds in Valenzuela) and present data which Is generalisable to chronic wound in general. In addition The EAC report overview (pg 226 supporting documentation) conclude that "that the results would be generalisable to the UK setting as in all cases the population, settings and wound types and the approach to wound management are in line with how clinical experts have described UK practice" (pg 71 supporting document) and clinical expert opinion agreed with this. We would like to re-iterate the requirement to review evidence based on wound condition as progression to wound healing, as	Thank you for your comment. The committee carefully considered this comment and section 4.2 has been amended. The statement about narrow subgroups has been removed.

				reported in the EAC report and recently by the updated National Wound Care Strategy Programme. In the comparative studies the majority of the wounds were leg ulcers, this is representative of UK data as Guest 2020 reported that 67% of chronic wounds were Leg ulcers in table 1(1,054,000 out of 1,582,000 chronic wounds). The narrow subgroups described as “for example pressure ulcers, arterial leg ulcers, venous leg ulcers among others” these subgroups within the evidence cover all of the chronic wound types, Guest 2020 outlines the amount of chronic wounds as: Venous Leg Ulcers (560k wounds, 35% of chronic wounds), Leg Ulcer Unspecified (361k, 23%), Diabetic Foot Ulcers (326k, 21%), Pressure Ulcers (202k, 13%), Leg Ulcers mixed (102k, 6%) and Leg Ulcers arterial (31k, 2%). The single arm data which compares to base line in chronic wounds supports the comparative studies and should be considered as the updated national wound care strategy programme states that “accurate wound assessment is essential for monitoring wound healing, as wound size and wound bed status form baseline against which all subsequent treatment effectiveness will be measured” We would like to highlight that the EAC consulted with experts on the relevance of the evidence in section 8 of the EAC report (pg 71) “Clinical expert input suggests that chronic wound management approaches are likely to be similar regardless of wound aetiology therefore the EAC considers that results from studies including patients with wounds from mixed aetiologies are broadly generalisable while acknowledging some limitations.” We request the committee review this statement in line with how the data is representative of chronic wounds in the UK and to also consider the support the single arm studies offer the comparative evidence in line with national assessment programmes. Please again consider the role of wound condition as progression to healing.	
134	8	Healthcare professional	Clinical effectiveness (section 4.2)	I do not feel that this is a narrow sub group as all mentioned in the example are chronic wounds. These make up 70% of my work load in community. With the other 30% made up of lymphoedema assessments and post operative wound care.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Section 4.2 has been amended to reflect the committee discussion and this statement has been removed.

135	1	Healthcare professional	Clinical effectiveness (section 4.2)	I disagree that pressure ulcers, arterial ulcers and venous leg ulcers may be a narrow field. These types of wounds represents the vast majority of chronic wounds in my experience, not surgical wounds. The bulk of the primary or community care nurse time is taken up with exactly these types of aetiologies, so these are wholly representative of the chronic wound population and the burden on the NHS of wound care.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Section 4.2 has been amended to reflect the committee discussion and this statement has been removed.
136	5	Healthcare professional	Clinical effectiveness (section 4.2)	As a community based clinician we will encounter all types of wound. Our main patient base is chronic wounds vascular ulcers(venous and arterial) diabetic ulcers and pressure ulcers . These chronic ulcers amke up over 50% of the community caseload and aprox 65% of the case load patient care time, so it is not really a narrow subgroup to the community services. It is this patient groupwhere biofilms become problematic and where prontasan may be of greatest impact on augmenting wound healing. for completeness the rest of the wounds seen equate to about 37% acute post surgery wounds and 12 % that are non specific, similar to the Guest figures.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology. Section 4.2 has been amended to reflect the committee discussion and this statement has been removed.
	Clinical evidence – clinical experience				
137	8	Healthcare professional	Clinical evidence (section 3.1)	The total 792 of which 415 patient had prontosan, the 415 patients is equivalent to the whole total patient population of Barnsley Hospital. This is actually a really good clinically study representation.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
138	6	Healthcare professional	Clinical evidence (section 3.7)	Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust developed and implements a wound cleansing policy using prontosan on chronic wounds and acute wounds at risk of infection as 1st line in 2017. We have been able to achieve a 66% reduction in wound infection in our complex wound clinic using this principle. 2017 19/261 patients had a wound infection (7.3) and in 2020 2/78 patients had a wound infection (2.5%). The complex wound clinic review complex wounds including chronic wounds (more than 14 days old) e.g. leg ulcer, diabetic foot ulcers) and acute wounds at risk of infection e.g. surgical wounds, skin grafts. As a result in reduced infection rates, wounds are healing faster, less complications are seen, less nursing time is required as patients are either discharged or able to undertake self care.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.

				Due to the success that DBTH have seen from the policy this is being rolled out across the whole of Doncaster's health economy 1.7.21 for Practice Nurses, District Nurse and speciality services such as podiatry and dermatology.	
139	1	Healthcare professional	Clinical evidence (section 3.7)	As stated, saline has no active effect and that no comparative studies are relevant if there has been an 'introduction to Prontosan'. Clinical experience over a number of years with many many patients has shown a visual return to healthy granulation tissue, lifting and eradication of slough and a perceived stimulation the stagnant wound bed to either recommence healing or to proceed to heal. Dressing fibres have also been seen to be released from the floor of the wound and lift away from the wound bed once prontosan commenced.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
140	13	Healthcare professional	Clinical evidence	In my experience Prontosan is much more effective in wound cleansing than saline. In our local area we have implemented a Prontosan Wound Cleaning pathway and have had some outstanding results. We stagnant wounds the healing process has been much quicker. It promotes wound hygiene and allows effective clinical decisions ensuring excellent wound bed preparation.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
141	14	Healthcare professional	Clinical evidence	In our Trust, we have been using Prontosan solution for a number of years now and we have seen excellent results through its use. Unfortunately, these results are currently only anecdotal, as the data around Surgical Site Infections has not been routinely collected until recently. Hopefully we will soon be evidencing the efficacy of our Prontosan use through our own data. Working with B Braun representatives, we have developed a Trust Prontosan Pathway to assist our nursing staff with their wound cleansing. This pathway resulted from scrutinising a vast amount of evidence (over 35 quality clinical evidence papers including RCT's). As Tissue Viability Nurses we encourage all our nursing staff to cleanse all wounds with Prontosan, regardless of how they originated. It has been our experience that the application of Prontosan has greatly contributed to the reduction of infections, aided faster healing in wounds, prevented the build-up of a bioburden within the wound bed and assisted in the removal of biofilms.	Thank you for your comment. The committee values comments from clinicians about their experience using the technology.
142	16	Healthcare professional	Clinical evidence	As a trust we have been using Prontosan for 12 months, although as a practitioner I have been using for many years in previous trusts.	Thank you for your comment.

				Although not on our trust formulary at first, we have had remarkable success in improving patient outcomes for some challenging wounds. One of the first cases we used it on was a 54 year old gentleman with Toxic epidermal necrolysis that had affected his whole body, with significant impact on his genitals. Applying dressing to the area was impossible, the skin was raw, sloughy, painful and oozing with an increased risk of future infection. Prontosan soaks were applied to his scrotal area to enable gentle but powerful wound hygiene and in a week, the skin had completely healed in the area. In comparison to the rest of his skin where prontosan was not being used, the difference was outstanding. He had no pain in this process either and as he was able to apply this treatment topically himself, he felt in control and very pleased with the rapid over all outcome. No other dressings were used. Such was his joy in the product that he consented for his case to be written up in the future and to be used in the trust to highlight the benefits of the product, thus enabling me to get it onto our trust formulary. I have used Prontosan in this manner a number of times where dressings have not been possible, but the infection risk is very high or already present. Fournier's gangrene and necrotising fasciitis cases in particular this has been of huge benefit. In all these cases where wounds have been extensive, highly fragile, infected, painful and impossible to apply more traditional topical antimicrobial, I have found Prontosan soaks to be invaluable. They have been tolerated by the patient and been easy and quick for staff to apply- several of my patients have call it their wound 'spa' treatment! I have found the gel to be brilliant in pseudomonas cases, particularly in leg ulceration. One case in particular in the last 12months stands out with a lady with highly infected legs, suffering with huge amounts of pain affecting her mood and mental health. Undertaking dressings took up to 5 staff due to her anxiety, size and shape of her legs and wounds and her pain management. Initially various other topical antimicrobials were used in conjunction with IV antibiotics, but with little improvement. Some benefit was found with larvae therapy, but again, the pain of application and removal was great for her. In the end, prontosan gel was used as a primary layer with significant improvement. She became easier for staff to manage as her anxiety in dressing changes reduced and her pain became better managed, alongside to overall clinical improvement of her legs also.	The committee values comments from clinicians about their experience using the technology.

				There are many other cases where we have used prontosan and in all age ranges. I have used the product on neonates, on maternity cases, on dehisced abdominal wounds and in my previous trust where the product was well imbedded within the organisation, as a preventive measure for at risk patients such as major abdominal or complex orthopaedic surgery where infection risk was high and outcome would have been detrimental. This usage rather than saline, I believe has enable improved wound hygiene, reducing their infection risks, thereby reducing their hospital stays and improving their overall patient outcome. Prontosan's ability to move wounds forward enabling progression that not only supports earlier discharge, but reducing pain, and simplifying dressings for staff in complex cases to me makes it a valuable and cost affective product to have in my specialist tool box.	
	Clinical evidence – unpublished data				
143	2	Manufacturer	Clinical evidence (section 3.1)	Update – the study by Oropallo has now been peer reviewed and accepted for publication to be published on or around September 2021. We request this section is updated accordingly	Thank you for your comment. Section 3.1 and section 3.3 have been amended to reflect that the Oropallo study is now published.
Economic modelling (n = 7)					
144	2	Manufacturer	Recommendations (section 1.2)	In acknowledgement of the EAC report finding that "The economic modelling finds the use of Prontosan is cost saving based on a reduction in resources associated with a reduced time to healing or improvement in wound bed condition. The evidence base is limited but the model remains cost saving with a wide range of inputs" in addition the EAC reports that "the model is robust to variation" and also state that even when the Prontosan transition values match that of saline "no clinical benefit is modelled, the marginal cost is very small " The economic model demonstrates that when Saline transition probabilities are set as THE SAME AS SALINE (i.e. no effect) the additional cost is £146.84 per patient annually (if solution and gel is always used) or is solution alone is used the addition cost is modelled as £22.86. A mix of solution and gel would be used in reality in the NHS according to wound condition. The risk of introducing Prontosan is very small over the annual cost of wound care (Annual average costs for VLUs are reported in the literature as £7,600 on average, £3,000 for a healed VLU and ranging between £10,777 up to £14,475 for an infected VLU per year (Guest, Fuller, and Vowden 2018). In light of the level of robustness requested by the NICE committee can we ask them to consider the risk associated (£22.86-	Thank you for your comment. The committee has carefully considered this and decided not to make any changes to this paragraph. The committee agreed that the clinical and cost case were dependent on each other. Given that the clinical inputs in the model had either some concerns or were at high risk of bias and subject to the same uncertainty as discussed in the clinical evidence section, the committee concluded that the cost models are acceptable but any cost modelling using the available evidence is likely to be flawed.

				£146.84) in proportion to the cost of wound care and the cost savings with Prontosan use (£951.01).	
145	15	Specialist organisation	Cost evidence (section 3.9)	Disagree. Parameters are too wide for clear comparison, statistically based, not real life.	Thank you for your comment.
146	15	Specialist organisation	Cost evidence (section 3.9)	Until clinical evidence can be provided the costs cannot be assessed.	Thank you for your comment.
147	2	Manufacturer	Cost evidence (section 3.9)	This is a misrepresentation/understanding of the second model. This is wound bed condition model and model use of Prontosan for short term to improve the wound condition (as demonstrated in 2 RCTS). In the wound condition model Bellingeri was used to supply data for the model as it provided time (28 days) and quantifiable means (BWAT) to determine wound condition. The model represents short term use of Prontosan to achieve a good wound condition over 28 days. This would align to the additional information supplied in comments for section 4 around CQUINs and national wound assessment guidelines and local wound assessment tools which would be clinically informative for NHS practice, through 28 day wound assessments, the improvements seen with Prontosan over standard care of saline would be demonstrated from clinical inputs in wound assessment tools, which are completed as standard wound care practice. We request this sentence is amended in light of our clarification	Thank you for your comment. The EAC noted that the time horizon used was the time to reach a Bates-Jensen wound assessment tool (BWAT) score of 14. This was 4.1 weeks for the Prontosan group. After careful consideration, the committee decided not to amend the guidance. Please see additional responses elsewhere in this document regarding the use of the BWAT score.
148	15	Specialist organisation	Cost evidence (section 3.11)	Compared to what - very old data	Thank you for your comment. In section 3.11 the EAC concluded that Andriessen 2008 was the most suitable data source and provided the most robust estimates for wound improvement, deterioration and recurrence that reflected the clinical reality of treating chronic wounds.
149	2	Manufacturer	Cost evidence (section 3.10)	We would also like it to be acknowledged here that the EAC reported that “despite limitations the models were robust to variation in the clinical inputs, requiring only a small impact on time to healing or reductions in infections to remain cost saving”. The economic model demonstrates that when Saline transition probabilities are set as ‘the same as saline’ (i.e. no effect) the additional cost is £146.84 per patient annually (if solution and gel is always used) or is solution alone is used the addition cost is modelled as £22.86. A	Thank you for your comment. The committee considered this, and section 3.10 has been amended to include ‘The EAC acknowledged uncertainty in the cost modelling but noted that the approach was conservative.’

				mix of solution and gel would be used in reality in the NHS according to wound condition. The risk of introducing Prontosan is therefore very small over the annual cost of wound care (Annual average costs for VLUs are reported in the literature as £7,600 on average, £3,000 for a healed VLU and ranging between £10,777 up to £14,475 for an infected VLU per year (Guest, Fuller, and Vowden 2018). In light of the level of robustness requested by the NICE committee can we ask them to consider the risk associated (£22.86-£146.84) in proportion to the cost of wound care and the cost savings with Prontosan use (£951.01) when reporting on the economic model in line with the recommendation.	
150	2	Manufacturer	Cost modelling overview (section 4.10)	The models were robust to multiple sensitivity analysis performed by the EAC and the company and the EAC found the models were robust. The model using data from two different studies (Andriessen and Harding) report similar outcome effects demonstrating the RCT supporting the outcomes of the larger comparative study. If infection resolution rate is made the same for Saline and Prontosan the model still holds as a cost saving. When the transition probabilities for Prontosan are set to be the same as saline –the increased cost is estimates at circa £150 per year for use of solution and gel. If solution alone were use the cost of no impact would be £24.72, realistic use will be somewhere in between with gel used as required and not at all dressing changes see comments in 3.9 for more details and submitted models.	Thank you for your comment. Please see NICE's response to comment 144.
	Equality (n = 7 comments)				
151	9	Healthcare professional	Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?	None known	Thank you for your comment.
152	7	Healthcare professional	Are there any equality issues that need special consideration and are not covered in the medical	no	Thank you for your comment.

			technology consultation document?		
153	3	Healthcare professional	Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?	No	Thank you for your comment.
154	5	Healthcare professional	Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?	I think more consideration needs to be given to the patients with wounds that are unlikely to heal, or would be out of the 12 month time parameter, due to multiple co-morbidities, social and psychological aspects or palliative. it is the small improvements in the wound that will improve the quality of life, but only complete healing has been taken into consideration in this document. This will therefore limit the use of this product and the potential wound bed and quality of life improvements available to this patient group	Thank you for your comment. The committee considered improved wound bed condition as an appropriate outcome, especially for people that have wounds that take more than 12 months to heal or are unlikely to heal. Section 4.6 has been added to the guidance to reflect this discussion.
155	2	Manufacturer	Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?	Yes the current focus on wound closure, excludes the benefits from patients with wounds which may never heal. Wounds which never heal, can still benefit from improved wound condition and the aligned improved quality of life, which come from e.g. reduced exudate, odour and pain.	Thank you for your comment. Please see NICE's response to comment 154.
156	1	Healthcare professional	Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?	I need to highlight again that wound healing as the only outcome being considered here disadvantages the wounds which don't heal in a timely manner, and that measuring improved wound condition would benefit all chronic wounds and all patients. Having a optimum product which has been practically and clinically used over many years with success being recognised by NICE would only enhance the equality issue of all wounds .. and thereby the patient with that wound (despite healing potential) deserving the best treatment.	Thank you for your comment. Please see NICE's response to comment 154.

157	15	Specialist organisation	Are there any equality issues that need special consideration and are not covered in the medical technology consultation document?	Could lead to inequality due to variation in a HCP level of skill and training. Variation in care and best practice, patients may receive different care from staff due to time constraints.	Thank you for your comment.
Inaccuracies (n = 12)					
158	2	Manufacturer	Recommendations (section 1.2; rationale)	Fact check – Please can this wording be change to more accurately reflect the desloughing effect of Prontosan in addition to biofilm reduction as listed in the IFUs and in line with wording from 2.3 'innovative aspects'	Thank you for your comment. Please see NICE's response to comment 21.
159	2	Manufacturer	Clinical evidence (section 3.2)	This is inaccurate - table 12 (page 45 supporting documentation) from the EAC report concludes that: 1 RCT was low risk, 3 RCTs had some concerns and 1 RCT (Borges 2018 - excluded by the company for using only a single irrigation on VLU) was at a high risk of bias which should be expected due to the study design and limited clinical applicability. Please remove risk of bias reporting or change to reflect the risk of bias as assessed by the EAC "Risk of bias assessment revealed: 1 RCT was low risk of bias, 3 RCTs had some concerns and 1 RCT was at high risk of bias". We would to highlight that the 1 RCT at risk of bias (Borges) was a single irrigation and its clinical relevance is discussed in later comments within section 3.2. The remaining studies at low risk and some concerns are clinically relevant and support the use of Prontosan. We request the committee reconsider how they view the evidence in light of the risk of bias, clinical relevance of study to the scope and we request reference to "high risk of bias" be removed from the guidance. If this reporting of the data has factored in to the committee decision we ask that the evidence is re-reviewed accordingly.	Thank you for your comment. Section 3.2 has been amended to state that 1 trial was at low risk of bias, 5 had some methodological concerns and the remaining studies were at high risk of bias.
160	2	Manufacturer	Clinical evidence (section 3.7)	Inaccurate We request the committee change this to : Wound healing was reported in 2 studies (Harding 2012, unpublished and Andriessen 2008),	Thank you for your comment. This has now been amended to include Andriessen 2008.
161	2	Manufacturer	Clinical evidence (section 3.7)	Inaccurate, we request the committee change this to wound size in 3 studies (Romanelli 2010; Valenzuela 2008, Harding 2012, unpublished)	Thank you for your comment.

					Harding 2012, unpublished has been added.
162	2	Manufacturer	Clinical evidence (section 3.7)	Inaccurate CHANGE TO: and wound condition improvement in 2 studies (Bellingeri 2016, Valenzuela 2008). Velenzuela reports on significant improvements to many wound condition parameters in table 3 of the study including: exudate, slough, granulation, odour, oedema, stagnation (more details in the comment below)	Thank you for your comment. Valenzuela 2008 has been added.
163	2	Manufacturer	Clinical evidence (section 3.7)	Valenzuela reports significant improvements in wound condition which was acknowledged as wound healing by the EAC report: • in wound bed condition was reported after 2 weeks, compared with control regarding: stagnation (P=0.004), • increased granulation (P=0.013), • slough reduced (P=0.002), • presence of purulent exudate reduced (P=0.002), • malodour reduced (P=0.004), • oedema of perilesional skin reduced (P=0.000) • wound size (p=0.013) We ask the committee to change this sentence and highlight that a significant wound improvement wat observed in 2 RCTs for multiple wound condition parameter measures. As a general comment for this overall section regarding Prontosan compared with standard care we would like to highlight the below information and request the committee review adding this information here and reflecting again on the volume of evidence: Wound healing was reported in 2 studies (Harding 2012, unpublished and Andriessen 2008), wound size reduction (an indicator of wound healing progression) in 2 studies (Valenzuela 2008, Harding 2012, unpublished) and wound condition improvement (necessary for and an indicator of progression in wound healing) in 2 studies (Bellingeri 2016, Valenzuela 2008). Infection rate was reported in 2 studies (Harding 2012, unpublished, and Andriessen 2008) and clinical markers of infection in 1 study (Valenzuela 2008).	Thank you for your comment. Please see NICE's response to comments 160, 161, 162.
164	2	Manufacturer	Clinical evidence (section 3.7)	Inaccurate we request this is changed to: Infection rate was reported in 2 studies (Harding 2012, unpublished, and Andriessen 2008),	Thank you for your comment. Please see NICE's response to comment 160.
165	2	Manufacturer	Clinical evidence (section 3.7)	Inaccurate: Valenzuela shows significant reduction in microbiological cultures (P=0.004) and reduction in erythema (redness of surrounding	Thank you for your comment.

				skin, a clinical sign of infection) (P=0.004) in table 2. We request the committee amend this statement accordingly.	Section 3.7 of the guidance has been amended to include 'and a reduction in microbiological cultures and redness around the skin (Valenzuela 2008).'
166	2	Manufacturer	Clinical effectiveness overview (section 4.1)	The studies which compared saline to Prontosan in chronic wounds are: 4 RCTS and 1 non randomised comparative study. The EAC rated these studies as: 1 RCT of low risk of bias, the remaining 3 RCTs with some concerns and the non-randomised as high risk of bias. Two of the RCTs were and the non-randomised study reported large effect sizes. To report these studies as "low quality and at high risk of bias is inaccurate", we request the committee review this sentence	Thank you for your comment. Section 3.7 has now been amended.
167	1	Healthcare professional	Side effects and adverse events (section 4.4)	I don't understand as how granulation tissue improvements described can be a 'side effect' – granulation tissue as a % was a marker repeatedly reported on in the RCTs and observational studies – to demonstrate wound condition improvement.	Thank you for your comment. The subheading 'side effects and adverse events' has been removed from the guidance.
168	2	Manufacturer	Side effects and adverse events (section 4.4)	We query why plausible benefits is under the section title of side effect and adverse events as the pain reduction and improvement to granulation tissues are bot clinical benefits and not adverse events.	Thank you for your comment. Please see NICE response to comment 167.
169	2	Manufacturer	Side effects and adverse events (section 4.4)	Can we highlight that this may have been included under this heading in error clinical impact on the condition under side effects and adverse events. Improvements in the wound bed is an outcome requested to be reported on by the scope and is a clinical improvement and should be reported in the section title "clinical effectiveness" We request this sentence is moved out of side effects and adverse events. As with other request we re-iterate the need for the committee to address the role of wound condition in the progression of wound healing.	Thank you for your comment. Please see NICE response to comment 167.