10 November 2016
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Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Paediatric addendum on the CHMP guideline on clinical investigation of medicinal products for the treatment of acute heart failure' (EMA/CHMP/707532/2013)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	EFPIA
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1. General comments - overview

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	EFPIA welcomes the opportunity to comment on the on Paediatric addendum on clinical investigation of AHF. Here are some points for consideration when finalizing the document: • A set of definitions would be helpful to better define the scope of the guideline, as currently the guideline seems to invariably refer to Heart Failure, Acute Heart Failure, Acute Heart Failure Syndrome (e.g. intro lines 48-58) • A stronger clinical and pathophysiological discussion on disease would support the rationale for certain drug classes and endpoints better. This point seems to be of special importance in case the drug is not intended to be developed for adults with AHF so that no adult data will be available • Appropriate length of follow up period should be discussed as there might be increased midterm mortality • Length of ICU stay or hospitalization, time to listing for heart transplantation should be discussed and proposals to account for regional differences should be formulated.	Rejected. The points are noted and indeed highlight the variability in each of the parameters raised. The definitions are included in the main document and it is not considered expedient to repeat them here. The intent of the guideline is to focus on pharmacological treatment and thus on cardiac dysfunction accepting the fact that early surgical intervention often influences this variably. As discussion of surgical aspects of treatment are beyond the scope of this guideline. It is considered that parameters influenced by such factors need to be kept open. For example, ICU stay or hospitalisation are multifactorial and a categorical discussion of these is not considered helpful. Regional and within region differences are an inherent part of multicentre trials and standardisation of protocols would be the way forward. Didactic principles might actually hinder development and feasibility of studies. The duration of follow up is dependent on the disease and again this would be determined in the protocol.
2	According to the introduction in section 1, two main categories of AHF are recognised in children: HF due to	Partly accepted. As this is an addendum and should be read in conjunction with the

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	cardiomyopathies (i.e., muscle weakness) with parallels to the adult population; this guideline should discuss how to build on adult data for appropriate use in the pediatric population. On the other hand, there is high output failure with less adult parallels. It seems that the guideline should also address development in these conditions, as the lack of adult experience with both the disease and the treatment provides additional challenges. Finally, PDCO has approved a PIP (serelaxin EMEA-001168-PIP01-11-M02) for an adult AHF product in the related indication of AHF following surgical repair of a congenital heart defect. This condition has characteristics of AHF but also of acute lung injury and is sometimes referred to as 'pump disease'. Many products have been investigated in this condition, sometimes primarily in paediatric patients, suggesting a potential value of regulatory guidance. The current guideline should address whether and how development in this post-surgical condition can replace or supplement development in the two more traditional categories. The higher incidence of surgery could make this a relevant population, which also has adult parallels.	parent guideline, aspects that are important are discussed without being restrictive. It is up to each sponsor to take account of relevant aspect of each of the documents when planning the development programme. The issue of about post-surgical heart failure and complexities are recognised. However, it is considered that operative lung injury does not fall under the remit of this guideline and is therefore not discussed. A short note on inclusion of post-surgical heart failure patients is incorporated.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 48	1	It is acknowledged that AHF covers a very heterogeneous patient population both in terms of aetiology, age and, above all, clinical presentation. Considering the diversity of clinical presentation, the term "syndrome" therefore does not seem appropriate because the signs and symptoms of presentation vary depending on the age of the patient, the aetiology of the disease and associated abnormalities. Therefore it is suggested, not to use the term "Syndrome" but to refer to "Acute Heart Failure" in general.	Partly accepted. The heterogeneity implies that it is not a single disease and therefore the term syndrome is more appropriate as in the parent guideline.
Line 48	2	Comment: AHFS and AHF are used interchangebly in the 'parent' guideline. To avoid confusion, we propose to use AHF only. Proposed change (if any): AHF ~~Acute Heart Failure Syndrome (AHFS)~~	Accepted.
Lines 48-50	1	"In the paediatric population, the aetiology and pathophysiology of AHF is varied although some clinical manifestation may be similar. The main symptoms and clinical manifestations also differ."	Partly accepted. The proposal below could be confusing with two references to clinical manifestations being varied and similar.

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		Recommended change: "In the paediatric population, the aetiology**, ~~and~~** pathophysiology**, symptoms, and clinical manifestations** of AHF **~~is~~** varie**~~d~~d,** although some clinical manifestation**s** may be similar. **~~The main symptoms and clinical manifestations also differ.~~**"	
Line 54	2	Comment: Besides AHF the term HF is used. It is proposed to use AHF systematically, unless both AHF and chronic HF are meant.	Not accepted. AHF and CHF are categorised based on time element only and this distinction is becoming unclear. AHF often progresses imperceptibly to CHF. So the term is correct in the context of the sentence.
Line 59-64	1	This paragraph is confusing from a pathophysiological standpoint because it does not clearly distinguish between cardiac function and cardiac output (e.g. the cardiac output is indeed reduced in critical aortic stenosis but the cardiac function dramatically differs from a hypoplastic left heart). We would therefore suggest several different categorizations, for examples based on the presence and direction of an intra- or extra-cardiac shunt (none, L to R, R to L), low vs high cardiac output, low vs high cardiac function. Those pathophysiological categories can only guide therapeutic	Not accepted. The aim of the document is to provide guidance on pharmacological therapy. It would be unwise to treat this guideline as book on paediatric AHF. The distinction here based on the pharmacological interventions that help improve function such as muscle function and output. The suggested categorisation while correct pathophysiologically might be

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		strategies if considered separately and should not be grouped into a binary system.	accurate, is not considered helpful in the context of specific product development.
Line 65-67	1	HF after palliative surgery (e.g. Stage I, II or III palliation of HLHS) is a major unmet medical need and should be mentioned. The following language is suggested: “While definitive treatment of AHF in children often involves corrective surgery for congenital lesions or heart transplantation for end-stage cardiomyopathy, stabilisation with aggressive medical therapy for AHF before surgical treatment is of utmost importance both, as a short- to mid-term bridging therapy until corrective surgery or transplantation can be performed as well as a long-term treatment after palliative surgery (e.g. after stage I, II or III palliation for hypoplastic left heart syndrome).” In addition to the period before surgical treatment it is recommended to also consider and mention HF following surgery for congenital heart disease, e.g. postoperative low cardiac output syndrome.	Not accepted. The level of details and bridging is already included in the statement “medium to long term” and this has been updated. Further addition of specific examples is not considered essential.
Lines 67-70	1	It is understood that the overall aim of treatment of paediatric patients presenting with HF is to improve their short, medium and long term condition. However,	Not accepted. The artificial distinction between AHF and AHF progressing to CHF is purely one of definition

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		considering medium and long-term time horizons may imply treatment of CHF which may be beyond the scope of the present guideline. It may be helpful to specify that it is anticipated that treatment of paediatric AHF would typically involve shorter term pharmacological intervention, recognising that medium to long term stabilisation will also be key to assess B/R. Additionally, only short-term treatment goals are listed in the Guidance. We suggest to provide long-term treatment goals as well (e.g. myocardial remodeling allowing for growth-related improvement of cardiac function long-term (ACE-I treatment for AHF after closure of decompensated VSD), optimizing neuro-cognitive development).	based on time element. Clinical outcomes serve well as short, medium and long term goals. And these are included. The evidence for remodelling and particularly in relation to growth and use of neuro-cognitive development is considered problematic as it is influenced by a number of factors (including duration of anaesthesia, anaesthetic agents and their long term influence, time spent on CP bypass etc.).
Line 72	1	Suggest to remove the word “specifically”. Recommended change: “The pharmacological treatment of paediatric AHF is characterised by the use of drugs that may not have been adequately studied ~~**specifically**~~ in children.”	Accepted.
Line 72-74	1	The example of vasodilator use during fluid overload is very problematic; in many pediatric conditions of fluid overload and high output states vasodilators are contra-indicated (e.g. some vasodilators – NO, milrinone - are contra-indicated in	Not accepted.

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		AHF due to large L-R shunts and pulmonary hypercirculation; Fallot and pulmonary stenosis are examples of a high output state of the right-heart where vasodilators are not useful and in critical situations – hypoxic crisis – vasoconstrictors are even used). Suggestion to either name one specific example (e.g. systemic vasodilator like ACE-I in patients with compensated VSD) or remove the example all together.	
Lines 78-80	1	Comment: "The lack of specific trials in the paediatric population is multifactorial and related to the essential differences in aetiology of AHF between children and adults." Recommend change: "The lack of specific trials in the paediatric population is multifactorial. ~~**and related to the essential differences in aetiology of AHF between children and adults**~~. **There are** essential differences in aetiology of AHF between children and adults **as well as challenges in enrolment due to low patient numbers.**" As written originally, the second half of this statement is not accurate and should be removed. The lack of clinical trials in the paediatric AHF population is not a consequence of differences in aetiology between AHF in children and adults.	Partly accepted. The reason for deletion of the statement is not reasoned and so not accepted. Addition of enrolment difficulties is reasonable. The text has been modified to: *The reasons for lack of evidence based treatment modalities for paediatric AHF are many fold. The limitations for conducting clinical trials in paediatric AHF include relatively small patient numbers, varied aetiologies, the absence of well-defined clinical endpoints and a lack of consensus regarding optimal study design.*

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Lines 78-82	2	Comment: This text is confusing. There is not only a lack of trials in paediatric AHF; also in adult AHF new options are very limited. Old products predate paediatric regulations and fit the general profil of no studies in children. However, discussion of these issues may be beyond the scope of this guideline. (See also general comment on scope of the guideline).	Not accepted. Please see modified text above.
Line 82	1	"Some of the principles would be applicable to other forms of AHF." Recommended change: "Some of the principles would be applicable to other forms of **paediatric** AHF." Propose adding the word "paediatric" for clarity. Clarification would be welcomed as to which principles would be applicable to other forms of AHF.	Partly accepted. *It is a semantic change as this document relates to paediatric population.*
Line 83	1	There are cultural differences in the use of the Rx abbreviation, especially in Europe (some use it for "radiology" or "radiography", others for "prescription"). Recommend to spell out.	Accepted. Rx = Treatment

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Line 83	2	The subheading may be deleted.	Accepted.
Line 90-92	1	Industry conducts multicentre trials daily. Multicentre studies do not 'require' networks to be successful, though networks may advance the efficiency and quality of a multicentre study. Recommended change: ~~**These issues can only be addressed by**~~ Multicentre co-operation and the foundation of network**s** of paediatric cardiology centres willing to participate in clinical trials **can support the conduct of studies in paediatric AHF patients.**	Accepted.
94	2	Comment: This information seems trivial or is not understood. All product should be efficacious and safe in the target population.	Not accepted. This would be contradicting the paediatric legislation and requirement of data particularly in the paediatric population. Extrapolation is not always feasible and the paragraphs before discussed nuances of paediatric trials.
Lines 95-97	1	"The mechanisms may involve, blockade of renin-angiotensin-aldosterone system (RAAS), improving endothelial function, vasodilatation, anti-inflammatory, anti-arrhythmic and diuretic effects."	Not accepted. This text was removed from the introduction section of the Addendum.

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		Recommended change: "The mechanisms may involve multiple pathways such as~~:~~ blockade of the renin-angiotensin-aldosterone system (RAAS), increasing cardiac contractility, improving endothelial function**,** vasodilatation**,** anti-inflammatory, anti-arrhythmic and diuretic effects, reduction of vascular resistance and protection from organ damage during the acute heart failure episode." In addition to the other mechanisms listed that have shown demonstrable safety and efficacy in the paediatric population, drugs with the mechanism to increase cardiac contractility can improve cardiac output and have a positive benefit-risk ratio. Alternatively recommend deleting the list altogether as inherently not exhaustive and might not to take into account for evolving science.	
Lines 95-97	2	Comment: The guideline should apply to any mechanism of action. Proposed change (if any): ~~The mechanisms may involve, blockade of renin-angiotensin-aldosterone system (RAAS), improving endothelial function, vasodilatation, anti-inflammatory, anti-arrhythmic and diuretic effects.~~	Accepted.
Lines 93-94, 100-	1	"In view of these limitations, a guideline that addresses the	

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101		development of pharmacological treatment options in children is considered important." "In order to enhance the availability of medicinal products for paediatric use and to encourage data collection in the paediatric population including conduct of clinical trials, a guideline that outlines the requirements could be considered helpful." The two statements are inconsistent. The first states that a guideline is "considered crucial", while the second states that a guideline "could be considered helpful".	Partly accepted. This is not a point of debate- the need for a guideline is recognised. Text has been modified to: In view of these limitations, a guideline that addresses the development of pharmacological treatment options in children is considered crucial
Line 102	2	Proposed change (if any): ~~intended for use~~ or change to products intended for use	Accepted.
Lines 105-108	2	Comment: This sentence should be moved to section 7 Proposed change (if any): ~~Safety endpoints differ in children as compared to the adult population. They not only include hypotension, arrhythmias, need for prolonged ICU stay, but also changes in renal function, failure to thrive, growth retardation or delay in achieving expected mile stones.~~	Accepted. These safety endpoints are already listed in section 7 of the Addendum, under "Evaluation of safety", which is a dedicated section of the Addendum, therefore it is fully endorsed not to include these also in the Scope section 2. of the Addendum.

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Line 106-108	1	Proposed changes: "They not only include hypotension, arrhythmias, ~~need for prolonged~~ ICU **length of stay**, but also changes in renal function, failure to thrive, growth retardation or delay**s** in ~~achieving expected mile stones~~ **neuro-motor and neuro-cognitive development**. The term neuro-cognitive development englobes many more aspects of a healthy and meaningful life (e.g. social interaction, communication, learning) than the simple achievement of milestones (e.g. sitting, standing, walking).	Accepted.
Line 116	2	Comment: Reference should be made to the parent guideline (cf lines 43-46). Proposed change (if any): This is an addendum to the *Guideline on Clinical Investigation of Medicinal Products in the Treatment of Acute Heart Failure (CHMP/EWP/2986/03 Rev. 1)*. It is not meant as a guidance document on its own but rather highlights differences from adult patients with Acute Heart Failure (AHF) and points out paediatric-specific aspects.	Partly Accepted. It now reads: This is an addendum to the Guideline on Clinical Investigation of Medicinal Products in the Treatment of Acute Heart Failure (CHMP/EWP/2986/03 Rev. 1). It should be read in conjunction with the introduction and general principles of the Annex I to Directive 2001/83/EC as amended.
Lines 104, 136, 294	2	Comment:	Accepted.

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		Please write 'endpoint' consistently Proposed change (if any): ~~End point~~ endpoint	
Line 136	1	Recommend including the type of pediatric indications that may be studied. Refer to the Report on the Expert Group Meeting of Pediatric Heart Failure, EMA London in 2010 which states: **"**Types of paediatric HF – indications to be studied Aetiological subtypes of paediatric heart failure, recommended to be studied, include dilated cardiomyopathy, post-operative, low cardiac output heart failure, and failing Fontan procedure. Ventricular septal defect (VSD) with significant left-to-right shunt could not be studied in Europe as these patients are operated early in life. There is a consensus that safety data should not be extrapolated from adult population to children and from older to younger children as there is a high potential for errors. PK studies for heart failure drugs are needed for all ages before determining safety. Efficacy is considered difficult to be extrapolated due to feasibility limitations of fully powered trials using hard end-points." Proposed change (if any): The EMA should consider inclusion of the paediatric	Partly accepted. This expert group report is already referenced but that cannot serve as a regulatory / peer reviewed paper. It would not be feasible to include text as proposed as the indication will be acute heart failure amenable to pharmacological therapy. Specific conditions become restrictive. The text making reference to the Expert Group Meeting has been removed.

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		indications already discussed in the Expert Group report. Of note, the part highlighting the data should not be extrapolated from adults seems to contradict the last part of this guidance document (Section 7) which does suggest that extrapolation may be possible/considered. AHF should be defined and reference may be made to treatment guidelines, recommendation by “learned societies”	
Line 139	2	Comment: see below (4.3): the changes in cardiac function/ echocardiographic measurements are considered supportive only and are not considered appropriate as primary endpoint Proposed change (if any): ~~changes in cardiac function~~	Not accepted. It is not known what this refers to.
Lines 138-143, 148-152, 159-165	1	“They include mortality, cardiac transplantation, changes in cardiac function, time to step down care and clinical scores. It is recognised that all cause death and CV mortality events may not be frequent events in this paediatric population and other important parameters (e.g., reduction in the need of ventricular assist devices or referral for heart transplantation) assume greater significance and could be evaluated as measures of clinical benefit of a medicinal product.”	Partly accepted. The points listed could be used under specific circumstances although the evidence base as ever is not small. It is not considered helpful to include points that might cause large variation in quality of studies and inconsistent use of end points particularly in an addendum such as this.

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		Further endpoints of importance to be considered are: • LV assist device placement • ECMO – extracorporeal membrane oxygenation • Amount of vasoactive support, e.g. use of vasoactive score • Renal replacement therapy • Worsening of renal function/renal injury "Reduction in all- cause death or cardiovascular death, should be the primary goals of treatment of paediatric heart failure. There should be clarity in the definitions of each of these parameters and they should be objectively evaluated. While all-cause mortality would be the preferred endpoint, it is not anticipated that in this paediatric population all cause death will differ significantly from CV death as the population is unlikely to have complex co-morbidities in contrast to the adult population with AHF." "A delay in time to referral for transplantation (as an indicator of stabilisation of the clinical status) and, time to transplantation without other adverse consequences (e.g., reduced overall survival or end organ damage) could be measures of beneficial effect of the medicinal product. Time to actual transplantation is dependent of many factors including geographical location and organ availability but referral for transplantation using objective and pre-specified	The paragraph regarding efficacy endpoints has been reworded to: *The efficacy of pharmacological treatment modalities in paediatric AHF could be evaluated in clinical trials using any of the following parameters. They include mortality, time to specific events, use of ventricular assist devices, changes in cardiac function, clinical scores, symptom scores, duration of hospitalisation or ICU stay, hemodynamic measurements and biochemical parameters (see sections 4.1 – 4.6 below).*

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		criteria could be a useful indicator of success or failure of therapy with the medicinal product." The statement that reduction of death or cardiovascular death should be the primary goal of treatment is problematic and could lead to the interpretation of mortality being the primary study endpoint. Whereas saving lives is the ultimate treatment goal in many indications, the mortality, especially short-term during AHF episodes, is so low, that the primary treatment goal in most patients is hemodynamic stabilization, reduction of ICU and hospital length of stay, bridging to surgery/transplant and prevention of hospital-acquired complications, not reduction of mortality. Furthermore, the incidence being so low, there will never be enough cases to allow separate analysis of CV and non-CV deaths. Although, the guideline acknowledges that all-cause death and CV mortality "may not be" frequent events and that "other important parameters, such as reduction in the need for ventricular assist devices or referral for heart transplantation, may assume greater significance and could be evaluated as measures of clinical benefit of a medicinal product". However, the guideline ignores the challenges associated with using these endpoints as measures of efficacy in the paediatric AHF population. With regards to mortality measures, assessment in any rigorous fashion requires a large CV outcomes study and would involve at least several thousand patients followed for at least two	These arguments have been rehearsed on many occasions. As the text in the guideline does not mandate use of ACM or CV death as primary endpoints, there is option to consider other relevant endpoints. As the adult AHF has been considered different to paediatric AHF based on the argument presented previously, it is not possible to draw evidence of benefit automatically to the specific conditions.

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		years. Such studies are not feasible to conduct within a reasonable timeframe, given the size of the total population to be studied. Extrapolation of CV mortality data from the adult population to the paediatric population should be recommended rather than direct assessment of these endpoints as a primary measure of efficacy in the paedatric population. There is a need to consider novel endpoints and associated methodologies that combine a set of clinically important measures that will enhance the possibility to conduct a study. The endpoints may be defined based on the pharmacological properties of the compound, and signs/symptoms/clinical measures that are considered most relevant in the target population With regards to the non-mortality measures mentioned – such as cardiac transplantation, time in hospital, or need for VADs – these measures are often dictated by factors that are not generally expected to be modifiable by pharmacologic therapy and should not be recommended for an evaluation of efficacy in the paediatric AHF population. The guideline notes that "time to actual transplantation" is dependent on many factors including geographical location and organ availability but referral for transplantation using objective and pre-specified criteria could be a useful indicator of success or failure of therapy with the medicinal product". However, referral for transplantation is often dependent on the same	This text is contradictory to the suggestion of endpoints earlier in the comment (for example

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		factors as those affecting time to actual transplantation that are completely independent and unrelated to the success or failure of therapy. Non-mortality endpoint components are important to ensure feasibility of the trials having sufficiently statistical power to provide meaningful results.	need for VADs). The difficulties with referral to transplantation are well recognised; it is however considered possible to develop a scheme and criteria within the protocol for referral for transplantation. These points have been taken into account in the guideline text.
Lines 145-146	1	The introductory paragraph mentions “achieving expected milestones”, however, this should be more specific. Note: Similar language is also used in lines 107-108 and 290-291. Proposed change (if any): Suggest editing the text to say the following. “For younger children, achieving ~~expected~~ **neuro-developmental** milestones at appropriate times could also be relevant.”	Partly accepted. The text related to the safety endpoints (lines 107-108) has been deleted from the Scope section 2. (see previous comment, Lines 105-108) so this is N/A here; the change from “***expected milestones***” to “*neuro-motor and* ***neuro-cognitive development***” in the section 7. on “Evaluation of safety” has been incorporated in line with previous comment, Lines 106-108)
Line 146	2	Comment: Importance of non-invasive endpoints should be highlighted Proposed change (if any):	Not accepted. The reasons for addition of this statement are not strong. In paediatric HF units non-invasive measures of BP and SVR are not easy. With little babies being very fragile and susceptible to small fluctuations in these parameters, strong statements in guidelines are not

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			considered helpful. Hypothetical statement such as could be helpful for clinical or regulatory purpose will be misleading. **Also, this is already included in section 4.5- there is no reason to repeat.**
Line 148	2	Comment: There seem to be only advantages to focussing on all-cause mortality compared to CV mortality. It will avoid adjudication and definition issues, while the numbers are expected to be similar (and low). There could be an explicit preference for all-cause mortality compared to CV mortality.	Not accepted. No explanation is required here. Either ACM or CV mortality will be acceptable.
Lines 148-155	1	Following from the previous comment, the following text revisions are proposed: Reduction in ~~all-cause death or cardiovascular death,~~ **mortality** should be ~~the primary~~ **considered among the main treatment** goals ~~of treatment~~ of paediatric heart failure. ~~There should be clarity in the definitions of each of these parameters and they 149 should be objectively evaluated~~ Objective evaluation and/or adjudication of death cases should be considered. **Whereas** all-cause mortality ~~would be the~~ **is a** preferred endpoint **in adult AHF trials**, it is **not** anticipated that ~~in this paediatric population~~ all cause death will differ significantly from CV death **in the**	Partly accepted. The emphasis on mortality is lessened. The remaining changes are considered semantic and the final text proposal not meaningfully different to the current text and therefore the original text is retained. The paragraph has been updated to: *Reduction in all cause death or cardiovascular death, could be considered as part of the composite goals of treatment of paediatric heart failure. However it is recognised that*

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		paediatric population because complex co-morbidities are less common in infants and children compared to adults ~~as 151 the population is unlikely to have complex co-morbidities in contrast to the adult population with AHF~~. It is important to include sudden death (or death due to arrhythmia when documented) in evaluating mortality. On occasion, in cases of sudden death, there will be need for confirmation of absence of other causes and this may include a post mortem examination."	*mortality is a rare event in this particular context. It is important to include sudden death (or death due to arrhythmia when documented) in evaluating mortality. On occasion, in cases of sudden death, there will be need for confirmation of absence of other causes and this may include a post mortem examination. There should be clarity in the definitions of each of these parameters and they should be objectively evaluated.*
Lines 154-155	1	"On occasion, in cases of sudden death, there will be need for confirmation of absence of other causes and this may include a post mortem examination." Recommended change: "On occasion, in cases of sudden death, there will be need for confirmation of absence of other causes and this **may** include a post mortem examination." The coexistence of extra cardiac malformations in children with cardiac congenital defects is frequent. In this specific population, post mortem examination would always be desirable.	Not Accepted. While the reasoning is accepted, emphasis is not required. It should be recognised that Post-Mortem examination for the purposes of the clinical fact finding is different to PM for the purposes of the trial. Furthermore, the guideline is sensitive to differences in the possibility of obtaining PM examination globally.
Line 157-159	1	I: Duration of stay may be subject to variability which is	Accepted.

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		suggested to be added as proposed below. Duration of stay in intensive care unit (ICU) or duration of hospitalisation both indicate time to stabilisation (for step down care or discharge as appropriate) and they could be used as measures of efficacy of the medicinal product**.** **Duration of stay may be influenced by a variety of factors, such as regional or institutional variability, non-cardiac related factors and organizational aspects.**	
Line 165	2	Comment: There are multiple definitions of *worsening heart failure*. For this event, a definition should be included.	Not accepted. This guideline is the not the appropriate place for definitions of a clinical event. It is for the sponsors/ academics to propose a consistent definition. Standard definitions available from clinical guidelines could be adopted.
Lines 167-169	1	"Additionally, *time to referral for surgical correction of the structural abnormality* including valve surgery could be assessed as measure of effectiveness of the medical therapy as need for early surgery often indicates failure of medical therapy in the relevant population." Time to referral for surgical correction of the structural abnormality could depend on factors other than the success or failure of the medical therapy and is strongly biased by patient baseline characteristics, local availability of resources	Not accepted. While the sentiments are appreciated, the guideline needs to recognise there is a global development programme and often stringent criteria are not applicable. It is considered that this option should remain open and the appropriateness will be determined / detailed in the protocol.

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		or local practices. Indeed, this guidance states in its Introduction, “While definitive treatment of AHF in children often involves corrective surgery for congenital lesions or heart transplantation for cardiomyopathy, stabilisation with aggressive medical therapy for AHF before surgical treatment is of utmost importance, often in the intensive care setting”. As noted, the ultimate goal can be surgical, and the prescribing physician could refer the patient to corrective surgery, even if some benefit is conferred via the medical therapy. Of note, there are many patients with congenital cardiac disease for whom this is not an appropriate endpoint and that the current trend is toward earlier correction or modification of repairs often based on imaging modalities that indicate hemodynamic issues prior to development of symptoms.	
Line 171-179	1	Echocardiographic measures can provide useful information over longer periods of follow-up in chronic heart failure and can occasionally be critical elements to guide acute therapy (e.g. hypovolemia, tamponade). However, echocardiography is 1) classically very operator dependent and 2) is lacking sensitivity to detect subtle changes in cardiac function in the acute phase of cardiac function. For short-term follow-up of cardiac function during an AHF trial the clinically available information (vital signs – especially heart rate - peripheral perfusion, urinary output, laboratory – e.g. lactate, mixed venous O2 saturation) and hemodynamic assessments	Not accepted. This is rather related to chronic heart failure.

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		(invasive and non-invasive bedside monitoring) are much more sensitive and accurate and should be given priority over expensive, often sub-optimal (inter-operator variability, intra-individual variability due to extensive dressings, open chest post-surgery, ECMO cannulas, variability in volume status etc.) and resource-intensive echocardiography.	
Line 172	2	Comment: Introduction of imaging parameters as primary endpoint is not supported. The clinical relevance of such observations is not clear. Proposed change (if any): could be used as secondary or exploratory measures of efficacy	No accepted. This is misunderstood. There was no suggestion to use these as primary endpoints. They however are also not exploratory. So categorical statements are not included in the guideline.
Lines 172-174	1	"Similarly, ejection fraction or fractional shortening have been used as measures of left ventricular function and can be easily measured using echocardiography." Recommended change: "Similarly, ejection fraction or fractional shortening have been used as measures of left ventricular function and can be easily measured using echocardiography**, and also changes in heart rate correlate with improved ventricular function**."	Not accepted. The evidence of this is limited and moreover, when betablockers are used this change does not retain its so called" correlation". Therefore it tis not considered appropriate to include such a bold statement. The reference is helpful but would not really support use of heart rate as an endpoint is a

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		Reference to heart rate was missing, but is supported by latest literature. In chronic heart failure, patients with lower heart rates are associated with better outcomes. There may be a HR “paradox” in acute heart failure. In a paper published October 20,2015 in The International Journal of Cardiology, “Is there a heart rate paradox in acute heart failure” by Patricia Lourenco et al Reported results of 564 adult patients with acute heart failure followed for 12 months concluded, ”higher admission heart rate predicted survival advantage in acute heart failure. Patients presenting with tachycardia and discharged with controlled heart rate, had better outcome than those admitted non-tachycardic, or discharged with a non-controlled heart rate.”	condition where several intervention including pharmacological therapy could influence.
174/175	1	Proposed change (if any): Echocardiography should be performed following a pre-specified protocol and analysed by a blinded centralised laboratory with trained observers/readers, whenever possible. Multicentre trials may lead to great complexity if readers are not immediately accessible for interpretation.	Partly accepted. A modified version of the suggestion is incorporated. Terms such as whenever possible introduce subjectivity and hence not included. The text was modified to: *Echocardiography should be performed following a pre-specified protocol and analysed by a blinded, centralised laboratory with trained observers/readers.*
Lines 180-182	1	“When these parameters are used as endpoints, it is	Partly accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		anticipated that they will be linked to other hard clinical measures of outcome. At this present point in time, left ventricular remodelling has not been proven as a surrogate endpoint for medium to long term outcome." As part of the discussion on echocardiographic measures as efficacy endpoints, the guideline could address here the use of extrapolation studies, with explicit direction on how such studies can be performed using pharmacokinetics and echocardiography. As noted above, the statements "When these parameters are used as endpoints, it is anticipated that they will be linked to other hard clinical measures of outcome. At this present point in time, left ventricular remodelling has not been proven as a surrogate endpoint for medium to long term outcome", do not acknowledge that clinical outcomes are not feasible to assess as a primary endpoint in the paediatric AHF population.	The comment is noted and no change to the text is considered necessary. The lack of a link between remodelling and outcomes is recognised as is the difficulty for assessment. It is the sponsor's option to generate methods/ bridging links and therefore this is open to discussion.
Lines 180-182	1	"When these parameters are used as endpoints, it is anticipated that they will be linked to other hard clinical measures of outcome. At this present point in time, left ventricular remodeling has not been proven as a surrogate endpoint for medium to long term outcome." Hard endpoints are difficult to pursue in such small and heterogeneous populations. This text seems more to be a position (opinion) statement than providing feasible	Partly accepted. The feasible recommendations are to use clinical outcomes as endpoints and when alternates are deployed, it will be necessary to support their use with evidence that links any proposed endpoint to a clinical outcome. Fundamentally, the difficulty probably arises from interpretation and approach that hard end points are difficult to achieve.

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		recommendations. Cardiac function/hemodynamic measurement analyses may provide useful endpoints in a population likely to be waiting for surgery/transplant.	The text has been modified to: *When these parameters are used as endpoints, it is anticipated that they will be linked to clinical measures of outcome. At this present point in time, left ventricular remodelling has not been proven as a surrogate endpoint for medium to long term outcome.*
Line 183-189	2	Comment: This paragraph is more about patient selection or characterisation than about use for efficacy evaluation. Consider moving to section 5 or rewriting.	Not accepted.
Lines 183-189	1	"Section 4.4. Clinical or symptom scores" "Several clinical scoring systems are in use, which help classify or stratify patients according to severity of disease." Recommended change: "Several clinical scoring systems**, completed by the parent or caregiver when appropriate,** are in use~~, and~~ **which** help classify or stratify patients according to severity of disease."	Accepted. The comment is noted but no change is necessary as the text is open to use of any acceptable scoring system. The text been misunderstood in that scoring systems only use patients. The scores

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		Asking subjects less than 10 years of age about their symptoms is unlikely to yield reliable answers; this likely applies to children less than 12 years of age. If there are validated instruments to assess symptoms for younger children, please include a reference to these instruments. If not, propose clarifying that symptom scores can be ascertained through input from parents and care givers rather than patients.	mentioned are in clinical use. The comment only pertains those age groups who are very young and cannot express themselves well and the point that patients <10 or 12 years provide unreliable answers is incorrect and not agreed with.
Lines 191-199	1	"Often haemodynamic measurements are used especially in adult AHF as measures of efficacy in the proof of concept and dose finding studies. There is no mandatory requirement to evaluate invasive haemodynamic parameters in paediatric AHF and use of these should be guided by the clinical situation and aetiology of heart failure. In adults and in many cases in children, changes in haemodynamic measures such as pulmonary capillary wedge pressure (PCWP) or changes in ejection fraction are not linked to improved outcomes. Inotropic agents are good examples that produced statistically important changes in such parameters in the short term but resulted in poor outcomes. Therefore, it is important to link the medicinal product's effect on haemodynamic measures to clinical outcome measures such as mortality or removal of the need for transplantation." Recommended change: "~~**Often**~~**Though there can be**	Partly accepted. The comments and sentiments are noted. However, no change to the text is considered essential.

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		limitations to extrapolating haemodynamic effects to clinical outcomes, haemodynamic measurements are **often** used **(**especially in adult AHF**)** as measures of efficacy **or pharmacodynamic effect** in the proof of concept and dose finding studies. There is no mandatory requirement to evaluate invasive haemodynamic parameters in paediatric AHF and use of these should be guided by the clinical situation and aetiology of heart failure **such that use of invasive monitoring is appropriate**. In adults and in many cases in children, changes in haemodynamic measures such as pulmonary capillary wedge pressure (PCWP) or changes in ejection fraction ~~**are not linked**~~ **may not link** to improved outcomes. Inotropic agents are good examples that produced statistically important changes in such parameters in the short term but resulted in poor outcomes. Therefore, it is important to **have evidence** link**ing** the medicinal product's effect on haemodynamic measures to clinical outcome**s. Evidence may be developed directly or through other means such as extrapolation studies.** ~~**measures such as mortality or removal of the need for transplantation.**~~" It is acknowledged that registration trials require harder, i.e. more meaningful endpoints than for example the use of hemodynamic parameters or the level of hemodynamic support. There are many examples however in paediatric AHF where specific hemodynamic parameters are directly related	

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		to outcome (e.g. level of systemic vascular resistance after Norwood operation for hypoplastic left heart syndromes, level of pulmonary artery pressure after VSD repair) and where the level of hemodynamic support (whether medical or mechanical) immediately impact ICU and hospital length of stay, complications and morbidity/mortality. It is therefore suggested not to discard hemodynamic parameters based on evidence from the adult literature but to include them in the armamentarium of useful surrogate measures of harder outcomes or components of composite endpoints.	
Line 210-215	2	Comment: Rank-based endpoints should be addressed. Proposed change (if any): There is a need to develop more sensitive composite endpoints, e.g. rank-based endpoints. As long as regulatory experience is limited, applicants are adviced to seek scientific advice if such endpoints are foreseen.	Partly Accepted. A sentence about ranked composites is added.
Line 211-212	1	Consider the addition of the following text: “Combination of certain parameters either as a composite or co-primary endpoints offers some advantages when sample size is limited. **Ranked composite endpoints might**	Partly accepted. See above.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		further increase statistical power." **I:** The following addition should be considered: **Ranked endpoints reflecting clinical relevant categories can be considered and may provide increased statistical power over traditional morbidity / mortality endpoints.**	
Line 216-230	2	Comment: It is proposed to re-write this section, taking into account that there are two categories of patients as described in the introduction. Inclusion of patients with both low and high output failure should be considered. If any specific criteria apply for adolescent patients, these should be addressed. Moreover, in AHF, echocardiographic data from a stable situation may be unavailable. An acute echo may not be representative. This should be addressed when suggesting ulltrasound as important in selection of patients.	Not accepted. See below.
Line 217-218	1	As stated above in the comment to Line 171-179 echocardiography has limitations (inter-operator variability, intra-individual variability, lack of sensitivity) and should not be mandatory for AHF patient selection, as AHF is most often a clinical, not an echocardiographical diagnosis. In addition, cardiac MRI should be included as possible selection criterion in some specific cases.	Partly accepted. In paediatric AHF (except for cardiomyopathies), imaging is commonly used for establishing the diagnosis of the structural abnormalities and ventricular function. The limitations expressed here are common to all imaging modalities. Introduction of the word potentially is

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		Consider the addition of the following text: "The criteria and diagnosis of AHF should be based on baseline evaluation of functional or clinical scoring systems, **potentially** combined with echocardiographic parameters **or cardiac MRI**.""	misleading. Inclusion on MRI as a modality is well made. The text has been updated to: *The criteria and diagnosis of AHF should be based on baseline evaluation of functional or clinical scoring systems, combined with imaging such as echocardiographic parameters or cardiac MRI to establish structural abnormalities.*
Lines 227-230	2	Comment: The paragraph contains a duplication. Proposed change (if any): When conducting studies during adolescence, the aetiology of HF may vary depending on age, gender and ethnic background. ~~the age, ethnic background and gender differences~~ This should be taken into account as ~~the aetiology of heart failure in adolescents~~ it is different from ~~those occurring in~~ young children (where congenital heart defects are predominant). ~~In adolescents, the aetiology of myopathies may vary depending on age, gender and ethnic background~~.	Accepted.

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Line 235	2	Comment: Sometimes development may be targeted specifically at children Proposed change (if any): ~~As~~ If paediatric development (as usual~~ly~~) follows.	Accepted.
Lines 239-250 (Section 6.1)	1	Ontogeny in e.g. catecholamine receptors needs to be considered. Pediatric formulation should take poor absorption in AHF into consideration; therefore, an i.v. formulation could be the optimal one, or fast absorbing formulations. In addition, since many infants with AHF/CHF require tube feeding, compatibility with the tubing should be tested.	Not accepted.
Lines 252-253	1	There is reference to placebo controlled studies where feasible which seems unusual for paediatric studies. Proposed change (if any): Please clarify what is meant by “where feasible” (i.e. under what conditions/situations).	Comment noted. No change to the text is necessary.
Lines 256-259	1	“Such studies may be used to evaluate haemodynamic effect of the medicinal products (for specific circumstances and indications) but should include clinical parameters as endpoints in order such that they could function as supportive evidence of efficacy.”	Partly accepted. The definition of clinical parameters as endpoints has been made.

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		Recommend defining or providing examples of “clinical parameters as endpoints” in the context of exploratory therapeutic studies, the title of the section.	
Lines 265-266	2	Comment: Duplicate from 232-234 Proposed change (if any): ~~Therefore, it becomes necessary to maximise the information gathered from all other types of studies and the study designs need to be streamlined by use of specific principles~~.	Party accepted. This refers to confirmatory studies but taking into account available data for the indication/ disease etc. This is different to using Pk/ PD data and avoiding repetition. The text has been updated to: *Paediatric development needs to build on information on safety and efficacy of the medicinal product from the adult population. Information gathered from all other types of studies in children should be maximised including exploratory and PK studies conducted across groups. It is recommended to streamline the designs of these studies appropriately to facilitate collection of adequate information.*
Line 267	1	Are NYHA, PHFI or Ross HF classification the most relevant clinical scores in paediatric AHF?	Yes, they are considered relevant. No change to the text was made. Not accepted.
Line 269-271	1	Considering the heterogeneous aetiology and clinical	Partly accepted.

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		presentation of AHF it is often impossible to define a unifying set of diagnostic criteria; AHF is therefore often a clinical diagnosis that varies from one age category and from one of the many aetiologies to another. The suggestion is therefore not to make imaging or laboratory criteria mandatory for the diagnosis and staging of AHF in children, as they might not apply to all potential study participants, age groups or aetiologies.	Point noted. However, imaging is an essential element to establish the pathology/ structural anatomy. While the particular modality is not mandated, introducing words such as potentially encourages large variability and should be avoided.
Line 275	1	Should be "cardio"myopathy to distinguish it from striate muscle myopathies, like Duchenne.	Accepted. Sentence now reads: It is recommended that inclusion and exclusion criteria should be well defined to identify common functional characteristics (e.g. evidence of **cardio**myopathies or muscle dysfunction).
Lines 278-279, 283-284	1	“Use of an appropriate comparator is encouraged as placebo controlled studies may not always be feasible in this particular population.” “Placebo-controlled studies using add-on design to best standard of care are another possibility.” Suggest referencing local guidelines as a way to define standard of care (SoC) in the clinical study protocol.	Not accepted.
Line 281-283	1	It can be challenging to get a clinical trial approved on a	Point noted and has already been considered

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		National level that uses one investigational product and a comparator that is being used “off label” (thus constituting a second investigational product in “CTA” terms) without controlled data to support dosage or dose regimen in the paediatric population.	in the GL. No additional text is necessary.
Lines 287-291	1	“Safety evaluation in paediatric AHF is expected to be generally similar to adults with additional parameters that are important in children. These include parameters such as hypotension or low BP, arrhythmias, need for prolonged ICU stay, changes in renal function in addition to failure to thrive, growth retardation or delay in achieving expected mile stones and may all be relevant safety end-points.” As for the efficacy evaluation, safety analysis must be stratified by age, since drug metabolism and end-organ sensitivity is different. Safety "endpoints" also vary according to age: failure to thrive may be important for a toddler, and not for a 17 year old teenager. The same is true for physiological parameters such as heart rate. Cardiac output in infants is more sensitive to small heart rate reductions than in older children. As mentioned before, the coexistence of extracardiac malfunctions must be evaluated in children with cardiac congenital defects. The smaller populations studied may impair detection of	Partly accepted. The sentiments and comments are appreciated. As it has been stated, the development programmes (including parameters for efficacy and safety) should be tailored to the population under study and the disease. The issues are recognised and it is considered that additional restrictive text may not be helpful. The section has been revised to: *Safety evaluation in paediatric AHF is expected to be generally similar to adults with additional parameters (or endpoints) that are important in children. These include parameters such as hypotension or low BP (using age-appropriate definitions), hypoperfusion, arrhythmias, in addition to failure to thrive, growth retardation or delays*

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		differences in safety events between placebo and treatment groups. Thus a more stringent approach towards "safety signals" may be desirable.	*in neuro-motor and neurocognitive development and may all be relevant safety end-points. Measures of renal function such as creatinine or glomerular filtration rate may serve as safety end-points in paediatric AHF trials.*
Line 288-291	1	The term hypotension depends on how it is defined (no universally accepted definition available) and the use of a fixed threshold definition is problematic. Therefore it is suggested to use “hypoperfusion” as the most relevant safety endpoint, i.e. BP around or below the lower boundary of age-matched healthy control subjects that must be associated with signs of organ hypoperfusion (e.g. lactate increase, oliguria/anuria, clamped periphery, raising creatinine, reduced mixed venous O2 saturation or increased arterio-venous O2 extraction).	Partly accepted. There is no ideal expression that might be applicable here. Hypoperfusion could arise from various sources and may not be attributable to the drug. However, the comment is noted and some additional text proposed.
Line 290-291	1	Consider the following changes to the text: “...changes in renal function in addition to failure to thrive, growth retardation or delay in ***neuro-motor or neuro-cognitive development***.” Rationale see above for Lines 106 - 108.	Accepted. Change implemented as part of comment in lines 106-108.
Lines 296-307 48 57 86	2	Comment: This section contains only Abbreviations, no definitions.	Partly Accepted.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
60, 144 54, 56, 81, 84, 110, 165, 188, 194, 201, 228, 241, 269, 271, 272		AHFS, CM, LV and UCL occur only once in the text, so introduction of these abbreviations is not helpful. HF should be explained. AHF or HF could be systematically used instead of 'heart failure'. Proposed change (if any): ~~**Defini**~~**Abbrevia**tions ~~AHFS Acute Heart Failure Syndromes~~ ~~CM cardiomyopathy~~ HF Heart Failure ~~LV Left ventricular~~ ~~UCL University College London~~	
Line 319	1	Consider the following changes to the text: ***"D***T Hsu, Enalapril in Infants With Single Ventricle Results of a Multicenter Randomized Trial ~~Daphne~~;" Daphne is Dr. Hsu's first name.	Accepted.