

Propranolol in the treatment of infantile haemangiomas: lessons from the European Propranolol In the Treatment of Complicated Haemangiomas (PITCH) Taskforce survey

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Summary

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Conflicts of interest

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Background Oral propranolol is widely prescribed as first-line treatment for infantile haemangiomas (IHs). Anecdotally, prescribing practice differs widely between centres.

Objectives The Propranolol In the Treatment of Complicated Haemangiomas (PITCH) Taskforce was founded to establish patterns of use of propranolol in IHs.

Methods Participating centres entered data on all of their patients who had completed treatment with oral propranolol for IHs, using an online data capture tool.

Results The study cohort comprised 1097 children from 39 centres in eight European countries. 76.1% were female and 92.8% had a focal IH, with the remainder showing a segmental, multifocal or indeterminate pattern. The main indications for treatment were periocular location (29.3%), risk of cosmetic disfigurement (21.1%) and ulceration and bleeding (20.6%). In total 69.2% of patients were titrated up to a maintenance regimen, which consisted of 2 mg kg⁻¹ per day (85.8%) in the majority of cases. 91.4% of patients had an excellent or good response to treatment. Rebound growth occurred in 14.1% upon stopping, of whom 53.9% were restarted and treatment response was recaptured in 91.6% of cases. While there was no significant difference in the treatment response, comparing a daily maintenance dose of < 2 mg kg⁻¹ vs. 2 mg kg⁻¹ vs. > 2 mg kg⁻¹, the risk of adverse events was significantly higher: odds ratio (OR) 1 vs. adjusted OR 0.70, 95% confidence interval (CI) 0.33–1.50, *P* = 0.36 vs. OR 2.38, 95% CI 1.04–5.46, *P* = 0.04, *P*_{trend} < 0.001.

Conclusions The PITCH survey summarizes the use of oral propranolol across 39 European centres, in a variety of IH phases, and could be used to inform treatment guidelines and the design of an interventional study.

What's already known about this topic?

- Oral propranolol is widely prescribed as first-line treatment for complicated infantile haemangiomas.
- Anecdotally, prescribing practice differs widely, but no international survey has been undertaken to date.

What does this study add?

- This is the first European study of current practice in the use of oral propranolol in infantile haemangiomas, based on the largest case series of its kind.
- The PITCH survey confirms the overall efficacy and safety of propranolol, with the majority of paediatric dermatologists using 2 mg kg⁻¹ per day as a therapeutic dose.
- Any future clinical trial should therefore include a 2 mg kg⁻¹ per day treatment arm.

Haemangiomas are the most common benign tumour of infancy, with a postnatal incidence of around 5%.¹ In the latest International Society for the Study of Vascular Anomalies classification, infantile haemangiomas (IHs) are morphologi-

cally subdivided into focal or localized, segmental, indeterminate and multifocal IHs.² They typically develop during the first month after birth and follow a characteristic evolution from early rapid proliferation to a stabilization and a slow

involution phase, which often takes years. Around 20% of IHs need medical attention due to complications, for instance bleeding, ulceration or threat to vision.³

Since the serendipitous discovery of the benefit of propranolol in IHs in 2008,⁴ it has been rapidly adopted as the first-line treatment for complicated lesions, replacing oral corticosteroids. In addition to numerous case series and case reports, three randomized controlled trials have investigated the efficacy of propranolol in IHs, with the largest trial ($n = 456$) comparing a dose of 3 mg kg⁻¹ per day with 1 mg kg⁻¹ per day and placebo, which found that the higher dose was significantly superior with regard to treatment efficacy.⁵⁻⁷ However, this study used propranolol for a maximum of only 24 weeks, and excluded patients outside the proliferation phase as well as children with life- or function-threatening or severely ulcerated IHs for ethical reasons, owing to the inclusion of a placebo group.⁵ For instance, this would have excluded segmental IH (SIH). A dose of 2 mg kg⁻¹ of day is the most commonly reported dose in the literature, and between-centre heterogeneity in the use of oral propranolol in complicated IHs is likely, although no survey of clinical practice has so far been conducted across the European paediatric dermatology community to confirm this impression.^{8,9}

We therefore founded the Propranolol In the Treatment of Complicated Haemangiomas (PITCH) Taskforce in 2013 with three main objectives: (i) to ascertain patterns of propranolol prescribing in Europe, (ii) to collect data on the safety and efficacy of oral propranolol, and (iii) to help inform the formulation of treatment guidelines as well as the design of future interventional studies.

Patients and methods

Study data on patients who had treatment of an IH with oral propranolol were collected across eight European countries (Denmark, Germany, Ireland, Italy, the Netherlands, Spain, Sweden, and the U.K.) using the REDCap (Research Electronic Data Capture) electronic database tool (Vanderbilt University, Nashville, TN, U.S.A.).¹⁰ The study was conceived and coordinated by the Paediatric Dermatology Department at St John's Institute of Dermatology, Guy's and St Thomas' Hospital NHS Foundation Trust, London, U.K., and approved by the Research and Development Department at Guy's and St Thomas' Hospital NHS Foundation Trust.

Data were collected between June 2013 and November 2014. In the U.K., invitations to participate were disseminated through the British Society for Paediatric Dermatology membership list. Paediatric dermatology centres from seven other European countries were also invited to take part. Centres were asked to enter only patients who had completed propranolol therapy for an IH. The following data were collected: country of practice, specialty, patient sex, subtype of IH (focal, segmental or other type, including multifocal IH), treatment indication (periocular with threat to vision, nasal tip, causing functional disturbance, ulceration, recurrent bleeding,

uncomplicated IH on the face other than the periocular or nasal tip, parental request and other indication), age at treatment commencement, adjunctive therapies, preinitiation screening investigations, treatment dosage and duration, adverse events, treatment response (from 'excellent/complete response', 'good', 'poor' to 'none'), rebound growth and retreatment with propranolol. Where individual patient data were incompletely entered, we contacted the study centres to collect missing information.

We present primarily descriptive analyses. Age at treatment commencement, duration of treatment and the age at which therapy was stopped are presented as medians and ranges due to the non-normal distribution of the data. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated in relation to treatment response and risk of rebound growth. Following univariate analysis, significant risk estimates were mutually adjusted in logistic regression. The following variables were evaluated as potential confounders: sex, the age at which treatment was started, the length of treatment, the age at which treatment was stopped and the type of IH. The statistical analyses were conducted by C.F. and E.W. using SPSS software version 19.0 (IBM, Armonk, NY, U.S.A.). We followed the STROBE guidelines for the reporting of observational studies throughout.

Results

Data from 1097 patients were entered from 39 individual centres in eight European countries: Denmark (35 patients), Germany (193), Ireland (136), Italy (65), the Netherlands (23), Spain (92), Sweden (72) and the U.K. (481).

Patient demographics and clinical features

The majority (92.9%, 1018) of patients had focal IHs and were female (76.1%). The median age at initiation of propranolol was 17 weeks (range 0.5–396). 19.8% (217) of the total cohort were premature (defined as birth at < 37 weeks of gestation). In total 5.5% (60) had SIHs, and 0.8% (nine) multifocal IHs. Local investigators also entered data on 10 children treated with propranolol for a congenital haemangioma, but these cases were not included in the efficacy-related analyses as they are distinctly different from IHs. Of the focal IHs, 77.2% (786) had treatment initiated in the rapid growth phase, 21.5% (219) during stabilization and 1.3% (13) in the involution phase.

The three main indications for treatment were 'periocular location with threat to vision' (29.3%, 321), 'risk of cosmetic disfigurement on the face' (21.1%, 232) and 'ulceration and bleeding' (20.6%, 226). The other indications are displayed in Figure 1. At the time of initiation, 87.0% (954) were on no adjunctive treatment, while 6.1% (67) were taking oral glucocorticoids, 2.3% (25) were also undergoing laser therapy, 2.0% (22) were on topical glucocorticoids and 2.6% (29) were on 'other' therapies, including topical timolol.

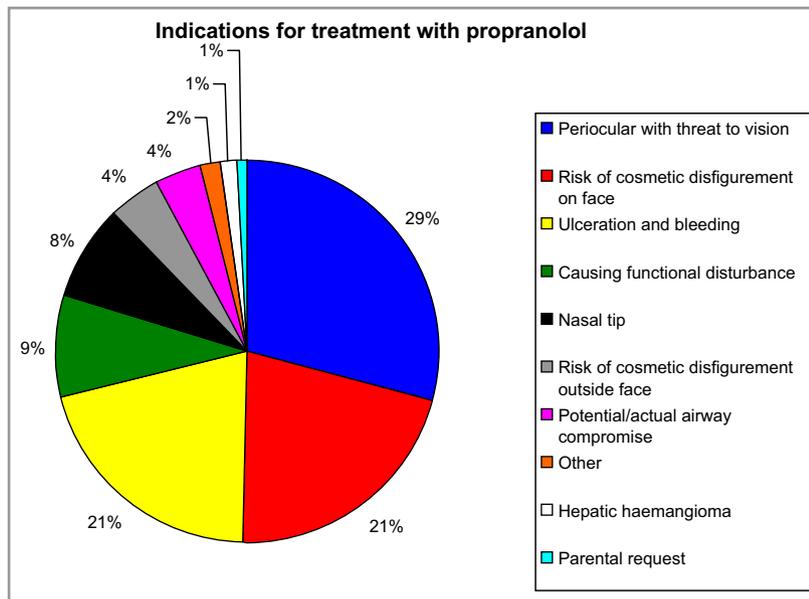


Fig 1. Indications for treatment with oral propranolol.

Preinitiation screening

69.1% (757) of patients had blood tests before starting propranolol, of whom 93.5% (708) had a glucose level, 88.8% (672) a full blood count, 86.0% (651) a renal profile, 82.0% (621) liver function tests and 61.8% (468) a thyroid profile. In total 92.3% (1013) underwent a cardiological or radiological investigation before starting propranolol. Some 88.5% (971) underwent an electrocardiogram (ECG), 67.5% (741) had an echocardiogram, 7.7% (84) magnetic resonance imaging and 15.7% (172) had an abdominal ultrasound. Most patients (98.4%) underwent a full clinical examination before treatment was started. Around half (54.9%, 602) had a specialist cardiology evaluation, and 50.4% (553) were also assessed by a general paediatrician.

Treatment initiation and dosage regimens

89.9% (985) of patients had propranolol initiated in a hospital setting: 44.2% (435) were day cases, 26.4% (260) had an overnight stay and 29.4% (290) had a hospital stay of two or more nights. The most common investigations undertaken during initiation were heart rate (98.3%, 968) and blood pressure monitoring (98.9%, 974), with 54.0% (532) also having glucose and 32.6% (321) ECG monitoring. 69.3% (759) of patients were started on a lower dosage and subsequently had dose incrementation to a maintenance regimen. The most frequent initiation dosage was 1 mg kg⁻¹ (47.2%, 517). In total, 18.6% (204) of patients were started at < 1 mg kg⁻¹ per day and 26.3% (288) at 2 mg kg⁻¹ per day. The majority of patients had a daily maintenance dose of 2 mg kg⁻¹ per day (85.7%, 939). Only 4.7% (52) of the cohort had a daily maintenance dosage of < 2 mg kg⁻¹. 9.4% (103) had a dosage of > 2 mg kg⁻¹. Most children were started on treatment during the rapid growth phase (71.6%, 785), but in a significant number treatment was initiated in the stabilization phase (20.0%,

219), and in a few even during the involution phase because of ulceration (1.2%, 13).

Treatment response and rebound growth

The median length of treatment was 32 weeks (range 2–184). One-fifth (19.8%, 215) of patients were reported to have an excellent response, compared with 72.0% (782) with a good response, 7.0% (76) with a poor response and 1.2% (13) with no response. There was a trend for a higher 'good or excellent' (vs. 'poor or no') treatment response in the groups receiving 2 mg kg⁻¹ per day (adjusted OR 1.25, 95% CI 0.43–3.62, *P* = 0.68) and the > 2 mg kg⁻¹ per day dose groups (adjusted OR 1.74, 95% CI 0.45–6.57, *P* = 0.42), but the results were statistically not significant, and there was no association with duration of treatment.

With regard to the phase of the IH when treatment was initiated, our results suggest that there is still benefit from treating patients in the stabilization phase, although the response rate was lower than in the rapid growth phase, with 18.3% of patients having a poor or no response compared with 5.6% of patients in the rapid growth phase.

Most patients (76.8%, 842) had their dose of propranolol titrated down before stopping. The median age at stopping was 56 weeks (range 4–412).

14.1% (154) of patients were reported to experience rebound growth of the IH after stopping treatment. Of those experiencing rebound growth, 53.9% (83) were restarted on propranolol, representing 7.6% of the total cohort. On retreatment, response was recaptured in the vast majority (91.6%).

Predictors of rebound growth

Although the median age when treatment was stopped was lower [52 weeks, interquartile range (IQR) 40–64] in the rebound growth than the 56 weeks (IQR 42–72) in the non-

rebound growth group, this difference was not statistically significant ($P = 0.08$, Table 1). The rebound growth risk reduction was most noticeable in the children who were aged ≥ 70 weeks when treatment was stopped (OR 0.58, 95% CI 0.34–0.99, $P = 0.048$), compared with children in the other age quartiles: up to 40 weeks (OR 1, reference group), 40–54 weeks (OR 0.83, 95% CI 0.50–1.37, $P = 0.46$) and 54–70 weeks (OR 0.90, 95% CI 0.55–1.48, $P = 0.68$; $P_{\text{trend}} < 0.001$). However, the results became nonsignificant for children aged ≥ 70 weeks when age at treatment initiation and treatment length were taken into account in multivariate logistic regression analysis. The results also did not appreciably change when the analyses were restricted only to children with focal IH or IHs in the rapid growth phase.

Segmental infantile haemangiomas

Our cohort included 60 SIHs. Of these, 35% (21) had an associated abnormality, with cerebral artery malformations, consistent with a diagnosis of PHACE syndrome, being the most common (15%, nine). Other associations are shown in Table 2. The median length of treatment for SIHs was 45 weeks (range 8–139). 32% of patients (19) showed rebound growth, compared with 13.1% for focal IHs (adjusted OR 3.33, 95% CI 1.85–6.01, $P < 0.001$). Ten patients (17%) were restarted on propranolol, and all of these recaptured their original treatment response.

Table 1 Predictors of rebound growth

Characteristic	Median weeks (IQR)		P-value
	Rebound growth (n = 154)	No rebound growth (n = 942)	
Age at treatment initiation	16 (9–28)	17 (12–28)	0.45
Age when treatment stopped	52 (40–64)	56 (42–72)	0.08
Length of treatment	32 (24–48)	32 (24–48)	0.12

IQR, interquartile range.

Table 2 Structural abnormalities associated with segmental infantile haemangiomas (SIHs, n = 60)

Structural abnormality	SIHs, n (%)
Cerebral artery anomalies	9 (15)
Posterior fossa abnormalities	4 (7)
Ventricular septal defect	3 (5)
Patent foramen ovale	3 (5)
Atrial septal defect	3 (5)
Sternal cleft/supraumbilical raphe	3 (5)
Coarctation of the aorta	2 (3)
Patent ductus arteriosus	1 (2)
Intracranial haemangioma	1 (2)

Adverse events

In total 19.6% (215) of the cohort experienced an adverse event, and these are shown in Table 3. Of those experiencing side-effects, 55.3% (119) continued with propranolol with the dose unchanged. One-quarter (25.1%, 54) had a dose adjustment, and treatment was stopped in 19.5% (42) of cases who experienced side-effects, which represented 3.8% of the PITCH cohort. The reasons for treatment cessation were wheezing (15), sleep disturbance (eight), diarrhoea (five), significant hypoglycaemia (four), worsening of the ulceration (four), persistent cough (two), irritability and poor feeding (one), concern about delayed development (one) and an episode of cyanosis (one).

The risk of experiencing an adverse event was more than twice as high in children on a maintenance dose of $> 2 \text{ mg kg}^{-1}$ per day compared with children on a lower treatment dose: $< 2 \text{ mg kg}^{-1}$ per day, adjusted OR 1; vs. 2 mg kg^{-1} per day, adjusted OR 0.70 (95% CI 0.33–1.50), $P = 0.36$; vs. $> 2 \text{ mg kg}^{-1}$ per day, adjusted OR 2.38 (95% CI 1.04–5.46), $P = 0.04$ ($P_{\text{trend}} < 0.001$). However, no individual category of adverse events made a significant stand-alone contribution to this risk increase. In addition, there was a $> 50\%$ lower rate of adverse events in the children who had their dose incremented compared with those who were started directly on the therapeutic dose: adjusted OR 0.48 (95% CI 0.35–0.65), $P < 0.001$.

Adverse events among children without baseline investigations

The necessity and depth of preinitiation screening is an area of uncertainty, and we therefore examined the adverse events and resultant changes in propranolol dosages during treatment in patients with preinitiation screening and those without. The adverse events in the groups with/without ECGs and echocardiograms prior to commencement were significant and are summarized in Table 4. Similarly, there was no significant difference in the frequency of other, noncardiovascular side-effects, such as hypoglycaemia, cold peripheries, sleep disturbance, diarrhoea and wheezing.

Table 3 Adverse events experienced while on oral propranolol treatment

Adverse event	Patients among total cohort, n (%)
Sleep disturbance	90 (8.2)
Cold peripheries	51 (4.7)
Wheezing	31 (2.8)
Diarrhoea	21 (1.9)
Symptomatic hypotension	18 (1.6)
Symptomatic hypoglycaemia	8 (0.7)
Symptomatic bradycardia	6 (0.5)
Other	36 (3.3)

Table 4 Adverse event frequency and resulting dose adjustments in those with/without preinitiation electrocardiogram and echocardiogram

	Echocardiogram			Electrocardiogram		
	Yes	No	P-value	Yes	No	P-value
Total patients	741 (67.5)	356 (32.5)	–	971 (88.5)	126 (11.5)	–
Adverse events (total)	148 (20.0)	67 (18.8)	0.67	186 (19.2)	29 (23.0)	0.28
Hypotension	13 (1.8)	5 (1.4)	0.67	15 (1.5)	3 (2.4)	0.48
Bradycardia	4 (0.5)	2 (0.6)	0.96	4 (0.4)	2 (1.6)	0.09

Values are n (%).

Discussion

The PITCH survey confirms the efficacy and safety of propranolol therapy in IHs, with a good or excellent response seen in over 90% of patients. Although there was a trend towards higher efficacy across the dose ranges, the difference between the proportion of good/excellent responses in the 2 mg kg⁻¹ per day and the > 2 mg kg⁻¹ per day dose groups was statistically not significant, whereas the risk of adverse events was significantly higher.

The PITCH Taskforce survey is the first international survey of its kind, collecting data from eight European countries, and to the best of our knowledge represents the largest single case series of children with complicated IHs treated with oral propranolol, although a previous systematic review collected data from 1264 patients included in 41 individual studies.⁸ Limitations of our survey include the retrospective nature of data collection, which has an inherent risk of reporting bias. Although we strongly encouraged individual study centres to enter all their patients who completed oral propranolol for an IH, there might have been patients with incomplete clinical records, where study centres therefore decided not to enter these patients into the study. It is also possible that the threshold of oral propranolol treatment for IHs changed over the years, as our experience and the published evidence of its efficacy has increased. This would have biased the early cases towards greater severity.

In addition, the classification of IHs is not straightforward, and this might have resulted in misclassification of some segmental and indeterminate IHs in particular. We also had no information on the depth and size of the IH, and side-effects were reported by physicians, not parents, which could have led to reporting bias. We were also not able to use more objective outcome measures, and there are no long-term follow-up data available on this cohort. Another limitation of our survey is that we included only patients who were treated with propranolol. We are therefore not able to say how many patients were not started on oral propranolol because of abnormal baseline investigations. However, the rate of side-effects in those who had no baseline investigations was comparable with the rate in those who had tests done prior to starting oral propranolol.

The strongest evidence for the efficacy of oral propranolol in IH so far comes from a recently published randomized con-

trolled trial that compared a dose of 1 mg kg⁻¹ per day with 3 mg kg⁻¹ per day, showing clear superiority of the higher dose in treatment efficacy.² However, we found no difference between 3 mg kg⁻¹ per day and the much more commonly used dose of 2 mg kg⁻¹ per day. Our results also suggest that IHs can benefit from oral propranolol treatment even during the stabilization phase, in line with other, smaller studies.^{11,12} Furthermore, ulcerated lesions are often refractory to a number of older treatment modalities,¹³ but may often respond well to propranolol, with 91.6% of IHs treated for ulceration/bleeding having a 'good or excellent' response. This high response rate is in keeping with other published evidence.¹⁴

As for potential side-effects, the PITCH survey suggests that treatment with propranolol is safe. Most reported side-effects were mild, with the most common side-effects being sleep disturbance and cold peripheries, accounting for 54% of all adverse events. Only 3.8% of our cohort ceased treatment due to side-effects. Hypoglycaemia was reported in only 0.7%, presumably because parents are advised to withhold propranolol at times of reduced oral intake.^{15,16} While adverse events were generally mild, little is known about potential longer-term side-effects. Propranolol is well known to cross the blood–brain barrier, and concerns have been raised over the drug's potential to lead to neurodevelopmental delay. Further research with long-term follow-up is required.¹⁷

In our cohort, there was a clear association between the frequency of adverse events and the treatment dose, with twice the number of adverse events seen in the 3 mg kg⁻¹ per day group compared with those receiving 2 mg kg⁻¹ per day or lower doses. Given the lack of significant difference in efficacy between these two doses, it seems prudent to use the lower dose, as long as the observed treatment effect is adequate. In addition, there was a > 50% lower rate of adverse events in the children who had their dose incremented compared with those who were started directly on the therapeutic dose (adjusted OR 0.48, 95% CI 0.35–0.65, *P* < 0.001), and dose up-titration is indeed recommended in current treatment guidelines.¹⁷

The need for in-depth investigations prior to commencement of propranolol remains another area of debate, and our data support a rationalization of pretreatment screening, in keeping with a recent European expert consensus statement.¹⁸ While initial recommendations suggested the need for full cardiological investigations with ECGs and echocardiograms,¹⁹

current US and European consensus guidelines state that full clinical examination and an ECG are sufficient.^{17,20} As we did not find a significant difference between rates of adverse events in those patients with pretreatment echocardiograms and ECGs vs. those who started without, apart from a slightly higher rate of bradycardia in those patients who did not undergo a pretreatment ECG (1.6% vs. 0.4%, $P = 0.09$), we feel that the additional value of an ECG, in the face of an unremarkable history and physical examination including auscultation, remains uncertain.²¹

With 60 cases, the PITCH survey assembled the largest case series of SIHs to date, with 15% of these patients having underlying cerebral vascular anomalies. There were similar rates of adverse events in this group when compared with the general cohort. 18% of patients with SIHs experienced side-effects, but in only 2% of cases did this lead to cessation of treatment. No cerebrovascular events were reported, and the efficacy and safety in this group were comparable with the rest of the cohort, although the risk of rebound growth was double that of the rest of the cohort, potentially due to the increased depth of these lesions.

Rebound growth was seen in 14.1% of the PITCH cohort. Those who were aged ≥ 17 months when treatment was stopped had a significantly lower risk of rebound growth in univariate analysis, but this effect was lost in multivariate regression analysis. Interestingly, when we stratified rebound growth rates by daily dosage, we found higher rates of rebound growth in the group treated with 3 mg kg⁻¹ per day: 27.5% vs. 13.0% at 2 mg kg⁻¹ and 16.0% at < 2 mg kg⁻¹. Our results may be explained by the type or size of IHs that necessitated a higher treatment dose. As for rebound growth rates, other studies found these to be between 5% and over 25%.^{3,22–26} Previous predictors of rebound growth after cessation of propranolol have included the size and depth of IHs and SIHs,¹⁴ which are variables we were not able to examine in this cohort.²⁷

In summary, oral propranolol has emerged as the first-line treatment for complicated IHs. Our large cohort study confirms that it can be used effectively and safely across a range of indications and phases of IH growth. Rebound growth is a significant risk, particularly in SIHs. However, we did not find that using propranolol at 3 mg kg⁻¹ per day reduced this risk significantly. As we found good efficacy across a range of dosages (1–3 mg kg⁻¹) with no significant difference in efficacy between 2 mg kg⁻¹ per day and 3 mg kg⁻¹ per day, the optimum treatment dose remains under discussion, also because the rate of side-effects appeared higher in children treated with 3 mg kg⁻¹ per day. An adequately powered randomized controlled trial comparing 2 mg kg⁻¹ per day with 3 mg kg⁻¹ per day is therefore required.

Author contributions

The PITCH Taskforce was initiated and led by Carsten Flohr. Emma Wedgeworth acted as Co-Principal Investigator. PITCH Taskforce Steering Committee: Carsten Flohr (Chair), Mary Glover, Alan Irvine, Hussain Shahidullah, and Emma Wedgeworth.

PITCH Study Writing Group: Eulalia Baselga Torres, Paula Beattie, Jesper Bjerre, Nigel Burrows, Tim Clayton, Carsten Flohr, Regina Foelster-Holst, Mary Glover, Angela Hernandez-Martin, Peter Hoeger, Iria Neri, Alan Irvine, Bisola Laguda, Tess McPherson, Arnold Oranje, Annalisa Patrizi, Jane Ravenscroft, Hussain Shahidullah, Ake Svensson, Carl-Fredrik Wahlgren, and Emma Wedgeworth. All co-authors were involved in the data collection. Carsten Flohr and Emma Wedgeworth wrote the manuscript, and all other co-authors critically revised the manuscript drafts.

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