IV fluids in children

Intravenous fluid therapy in children and young people in hospital

Appendix M December 2015

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Commissioned by the National Institute for Health and Care Excellence











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Funding National Institute for Health and Care Excellence

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Appendix M: Cost-sensitivity analysis: Monitoring and assessment strategies for intravenous fluid therapy in children

M.1 Introduction

The monitoring of fluid balance in children could include the measurement and recording of weight as well as the recording of fluid balance (including all input and output) on a fluid balance chart. Well performed and recorded monitoring is important as this may prevent the occurrence of fluid-related complications. Monitoring should be performed at regular intervals and at an optimum frequency since this information may tailor intervention. However, excessive monitoring may increase costs unnecessarily and may provide little additional health benefit.

The systematic clinical review did not identify any evidence for the optimal monitoring strategy for IV fluid therapy in hospitalised children. Also, no studies were identified from published literature that assessed the cost effectiveness of different monitoring frequencies and strategies. Thus, the GDG judged that an economic analysis would be useful to help inform recommendations on optimal monitoring. A cost-effectiveness analysis was not possible due to the absence of effectiveness data. Therefore a cost-sensitivity 'threshold' analysis was selected as a feasible and informative approach. In this analysis we present the number of complications and critical care episodes required for cost neutrality of various monitoring strategies versus 1) the cheapest strategy, 2) current practice.

M.2 Methods

M.2.1 Overview

A threshold analysis was undertaken to identify the number of fluid associated complications that must be prevented in order for various monitoring strategies to be cost neutral.

Nine monitoring strategies were selected for comparison (Figure 1), ranging from no weight measurement and no fluid balance recording (Strategy 1), to weight measurement twice daily as well as complete fluid balance recording (Strategy 9).

Figure 1: Monitoring strategies compared in the analysis

		None	Partial	Complete
	None	Strategy 1	Strategy 2	Strategy 6
Weight measurement	Twice weekly		Strategy 3	Strategy 7
	Daily		Strategy 4	Strategy 8
	Twice daily		Strategy 5	Strategy 9

Fluid balance recording

The population included for the analysis was children in hospital requiring IV fluid therapy for maintenance of fluid balance. Monitoring and assessment strategies described here are not suitable for patients undergoing fluid resuscitation because of their unique fluid and electrolyte requirements.

We first calculated the cost of each monitoring strategy, then we estimated the number of adverse events that would need to be prevented so that a monitoring strategy would be cost neutral compared to:

- 1. the monitoring strategy with the lowest cost (Strategy 1),
- 2. the monitoring strategy which best represented current practice (Strategy 3).

Key assumptions

1. Weight measurement:

a. All weighing scales and equipment for weight measurement of mobile, partially mobile, immobile and complex (for example spinal) patients are available in hospital.

b. Sanitisation costs for equipment are negligible for all weight measurement equipment and as such were excluded from analysis.

c. All children are weighed on admission, unless the strategy is a 'no weight measurement' one. Hence, where the length of IV fluid administration is less than 4 days, the twice weekly weighing strategies include only one instance of weight measurement.

2. Fluid balance recording:

a. Costs of additional stationary (fluid balance charts and pen) required across monitoring strategies are negligible and as such were excluded from the analysis

3. Ward nurses (AfC band 5) and Clinical support workers (or equivalent at AfC band 2) are responsible for performing weight measurement. Fluid balance chart completion is carried out mainly by ward nurses (AfC band 5).

4. The duration of IV fluid therapy was assumed to be on average 2 days. This assumption was based on the GDG expert opinion and was examined in sensitivity analysis using shorter (1 day) and longer (3 days) durations.

M.2.2 Inputs

M.2.2.1 Resource use and cost

The cost of each monitoring strategy was the sum of the costs of two assessment components, weight and fluid balance, over the period of IV fluid administration.

Fluid balance recording

The cost of fluid balance recording included manpower costs only as stationary costs were estimated to be negligible. The unit costs of staff time are reported in Table 1 below.

Table 1: Unit costs of staff time

Healthcare professional	Cost (£)/ hour	Cost (£)/ minute	Source
Clinical support worker (CSW) ^(a)	£21	£0.35	PSSRU 2013 ¹

Healthcare professional	Cost (£)/ hour	Cost (£)/ minute	Source
Ward nurse ^(b)	£41	£0.68	PSSRU 2013 ¹

(a) PSSRU description: Clinical support worker (hospital) Agenda for Change Band 2, 2012/13

(b) PSSRU description: Nurse, day ward (includes staff nurse, registered nurse, registered practitioner) Agenda for Change band 5, 2012/13

A complete fluid balance chart contains all fluid input/output components, while a partially completed fluid balance chart contains only fluid input components. The GDG experts estimated that a ward nurse would fill in 90% of the fluid balance chart while the remaining 10% would be completed by a clinical support worker. They also estimated that the physical act of complete recording of fluid balance for any hospitalised patient would take hospital staff 5 minutes per hour (120 minutes per day), while partial recording (recording fluid inputs only) would take 3 minutes per hour (72 minutes per day). The adding up of the fluid chart components would take 5 minutes per calculation; assuming hourly totals are already calculated. This calculation is completed twice in every 24-hour period and is undertaken by a ward nurse. Using these estimates and unit costs for health care professionals' time in Table 1, a total of 130 minutes was required for complete fluid balance recording every 24 hours and the resulting cost was £84.44, while a total of 82 minutes was required for partial fluid balance recording every 24 hours with a resulting cost of £53.38 (see Table 2).

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Healthcare professional	% undertaken by staff member ^(a) (A)	Minutes required per 24 hours ^(a) (B)	Cost per minute ^(b) (C)	Total cost per 24 hours = A*B*C			
Filling-in (partial FBR)							
Ward nurse	90%	72	£0.68	£44.06			
Clinical support worker	10%	72	£0.35	£2.52			
Total (D)				£46.58			
Filling-in (complete FBR)							
Ward nurse	90%	120	£0.68	£73.44			
Clinical support worker	10%	120	£0.35	£4.20			
Total (E)				£77.64			
Adding-up							
Ward nurse	100%	10	£0.68	£6.80			
Total (F)				£6.80			
Total cost for partial FBR (D + F)				£53.38			
Total cost for complete FBR (E + F)				£84.44			

Table 2: Breakdown of daily cost of fluid balance recording (FBR) per patient

(a) Based on GDG opinion(b) See Table 1

Weight measurement

The cost of weight measurement was based on the amount of time required to weigh a patient and the number and type of staff members required for the process, which may differ according to the condition of a patient. According to GDG estimates, the process of weight measurement ranges from 10 to 36 minutes and requires 2 to 5 hospital staff members including at least one qualified nurse. When measuring the weight of a complex patient (for example spinal), 5 staff members trained in spinal care would be required. The total cost of weight measurement for a hospitalised patient was £13.53, calculated as the weighted average of the 4 patient categories in Table 3. Weights were

assigned according to estimates of the proportion of hospitalised patients expected to be in each patient category based on GDG opinion.

Patient category	Proportion of hospitalised patients	Number of Clinical Support Workers (CSWs)	Minutes required from CSW	Number of ward nurses	Minutes required from ward nurse	Cost per patient (£)	Weighted cost (£)
Mobile patient	70%	1	10	1	10	£10.30	£7.21
Partially mobile patient	20%	1	15	1	15	£15.45	£3.09
Immobile patient	9%	2	20	1	20	£27.60	£2.48
Complex patient (for example spinal)	1%	4	36	1	36	£74.88	£0.75
Weighted average cost per weight assessment							£13.53

Table 3:	Breakdown of the cost of weighing a patient
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Fluid-related complications

The cost of an IV fluid-related major complication was calculated as a weighted average of all NHS reference costs 2012-2013 for fluid and electrolyte disorders relating to paediatric non-elective inpatient long stay categories KC05 G, K and L. Each category was weighted according to the number of documented admissions. The result was £3,799 for an average total length of stay of 6.7 days.²

M.2.3 Computations

Since we are only considering the manpower costs of monitoring strategies and the cost of major complications we can say that the cost of strategy m is:

$$C_m = C_m^{wfc} + C^{comp} N_m$$

Where

 C_m^{wfc} is the cost of weighing and fluid balance recording associated with monitoring strategy m,

C^{comp} is the cost of a major complication

and $N_{\rm m}$ is the number of complications associated with monitoring strategy m.

For a second monitoring strategy L to be cost neutral it follows that:

 $C_m = C_L$ and

 $C_m^{wfc} + C^{comp} N_m = C_L^{wfc} + C^{comp} N_L$

By re-arrangement, the formula for the number of complications that would need to be prevented in order for monitoring strategy m to be cost neutral compared with monitoring strategy L, is:

 $N_m - N_L = (C_L^{wfc} - C_m^{wfc}) / C^{comp}$

M.2.4 Sensitivity analyses

Sensitivity analysis 1

The cost of a critical care episode was added to the cost of a complication in another sensitivity analysis. It was calculated as the weighted average of all NHS Reference costs 2012-2013 for all episodes of neonatal and paediatric critical care (XA01-XA06 and XB01-XB09).² Each category was assigned a weight according to the number of documented days. The cost per critical care period was £764 and the total cost of a complication was £4,563, compared to £3,799 in the base case.

Sensitivity analysis 2

The variation in a patient's condition may affect the time required for fluid balance recording. To address this uncertainty the time estimate for filling-in a fluid balance chart was changed to double its base case value for both partial and complete fluid balance recording. The resulting figures are reported in Table 4.

Healthcare professional	% undertaken by staff member ^a (A)	Minutes required per 24 hours ^a (B)	Cost per minute ^b (C)	Total cost per 24 hours = A*B*C
Filling-in (partial FBR)				
Ward nurse	90%	144	£0.68	£88.13
Clinical support worker	10%	144	£0.35	£5.04
Total (D)				£93.17
Filling-in (complete FBR)			
Ward nurse	90%	240	£0.68	£146.88
Clinical support worker	10%	240	£0.35	£8.40
Total (E)				£155.28
Adding-up				
Ward nurse	100%	10	£0.68	£6.80
Total (F)				£6.80
Total cost for Partial FBR (D + F)				£99.97
Total cost for Complete FBR (E + F)				£162.08

Table 4: Cost of fluid balance recording (FBR) in Sensitivity Analysis 2

(a) Based on GDG opinion

(b) See Table 1

Using this assumption, the resulting time required for complete FBR per 24 hours was 250 minutes with a total cost of £162.08 (compared to £84.44 in the base case), and for partial FBR, time required per 24 hours was 154 minutes with a cost of £99.97 (compared to £53.38 in the base case).

Sensitivity analysis 3 (a and b):

In the base case analysis, it was assumed the average duration of IV fluid administration is 2 days. This assumption was examined in sensitivity analysis where shorter (1 day – sensitivity analysis 3a) and longer (3 days – sensitivity analysis 3b) durations were used instead.

M.3 Results

M.3.1 Base case and sensitivity analysis 1

Table 5 below provides the base case results for comparisons of each monitoring strategy versus Strategy 1 (the lowest cost strategy) and Strategy 3 (the strategy most similar to current practice in the general ward).

The cost of a monitoring strategy of 2 days duration ranges from £0, if there is no monitoring and assessment, to £224 if the monitoring strategy requires weight measurement twice a day and includes complete fluid balance recording (Strategy 9).

The number of complications that Strategy 9 would need to avert for it to be cost neutral compared to the cheapest strategy (Strategy 1) would be 59 per 1000 patients. When critical care costs are included, the number of complications that would have to be prevented would reduce to 49 per 1000 patients.

The GDG advised that current practice for monitoring and assessment is most similar to Strategy 3, weight measurement twice a week and partial FBR. The cost differential between Strategy 3 and Strategy 1 is £120 and current practice would need to prevent 32 complications per 1000 patients (26 including critical care costs) to render it cost neutral. Of the six monitoring strategies that are more costly than current practice (Strategies 4 to 9), the greatest incremental cost difference is £103, associated with Strategy 9. For this strategy to be cost neutral, it would need to prevent 27 complications (per 1000 patients) more than current practice (23 including critical care costs).

M.3.2 Sensitivity analyses 2 and 3

If the estimated time required for FBR is increased to double its original values (250 minutes per day for complete FBR and 154 minutes per day for partial FBR), the cost of monitoring strategies will range from £0 to £378 (Table 6). In this case, the most intensive monitoring strategy would need to avert 100 (83 including critical care costs) major complications per 1000 patients to be cost neutral. To be cost neutral compared to current practice, Strategy 9 would need to prevent 43 more complications per 1000 patients (36 including critical care costs). The results of the sensitivity analysis examining the impact of assuming a longer and shorter duration of IV fluid administration (3 and 1 days) are presented in Table 7 and Table 8, respectively. The results show that with a longer duration, the cost of monitoring strategies ranges from £0 to £335. In this case, the most intensive monitoring strategy (Strategy 9) would need to avert 88 major complications per 1000 patients (73 including critical care costs) to be cost neutral compared to Strategy 1. To be cost neutral compared to current practice (Strategy 3), Strategy 9 would need to prevent 42 more complications (35 including critical care costs) per 1000 patients. If IV fluids are to be administered for 1 day, the cost of monitoring strategies ranges from £0 to £112. In this case, the most intensive monitoring strategy (Strategy 9) would need to avert 29 (24 including critical care costs) major complications per 1000 patients to be cost neutral compared to Strategy 1. To be cost neutral compared to current practice (Strategy 3), Strategy 9 would need to prevent 12 more complications (10 including critical care costs) per 1000 patients.

Table 5: Base case and sensitivity analysis (1) results

Stra	rategy		Cost over the duration of IV fluid		Number of extra complications that would have to be prevented per 1000 patients to make strategy cost neutral		Sensitivity analysis 1: Number of extra complications that would have to be prevented per 1000 patients to make strategy cost neutral (including critical care costs)		
#	Weight measurement	Fluid balance recording (FBR)	Weight measurement	Fluid balance recording (FBR)	Total	Compared to Strategy 1	Compared to Strategy 3	Compared to Strategy 1	Compared to Strategy 3
1	None	No FBR	£0	£0	£0				
2	None	Partial FBR	£0	£107	£107	28		23	
3	Twice weekly	Partial FBR	£14 ^(b)	£107	£120 ^(c)	32		26	
4	Daily	Partial FBR	£27	£107	£134	35	4	29	3
5	Twice daily	Partial FBR	£54	£107	£161	42	11	35	9
6	None	Complete FBR	£0	£169	£169	44	13	37	11
7	Twice weekly	Complete FBR	£14 ^(b)	£169	£182 ^(c)	48	16	40	14
8	Daily	Complete FBR	£27	£169	£196	52	20	43	17
9	Twice daily	Complete FBR	£54	£169	£223	59	27	49	23

(a) IV fluids administered for 2 days

(b) The cost of one-off weight measurement on admission is included in the twice weekly weight recording strategies

(c) Difference due to rounding

Stra	Cost over the duration of IV fluidrategyadministration ^(a) (£)			Number of extra complications that would have to be prevented per 1000 patients to make strategy cost neutral		Number of extra complications that would have to be prevented per 1000 patients to make strategy cost neutral (including critical care costs)			
#	Weight measurement	Fluid balance recording (FBR)	Weight measurement	Fluid balance recording (FBR)	Total	Compared to Strategy 1	Compared to Strategy 3	Compared to Strategy 1	Compared to Strategy 3
1	None	No FBR	£0	£0	£0				
2	None	Partial FBR	£0	£200	£200	53		44	
3	Twice weekly	Partial FBR	£14 ^(b)	£200	£213 ^(c)	56		47	
4	Daily	Partial FBR	£27	£200	£227	60	4	50	3
5	Twice daily	Partial FBR	£54	£200	£254	67	11	56	9
6	None	Complete FBR	£0	£324	£324	85	29	71	24
7	Twice weekly	Complete FBR	£14 ^(b)	£324	£338	89	33	74	27
8	Daily	Complete FBR	£27	£324	£351	92	36	77	30
9	Twice daily	Complete FBR	£54	£324	£378	100	43	83	36

Table 6: Results of sensitivity analysis (2) assuming longer time involved in fluid balance recording

(a) IV fluids administered for 2 days

(b) The cost of one-off weight measurement on admission is included in the twice weekly weight measurement strategies

(c) Difference due to rounding

Strategy		Cost over the duration of IV fluid administration ^(a) (£)			would have to be	complications that e prevented per make strategy cost	Number of extra complications that would have to be prevented per 1000 patients to make strategy cost neutral (including critical care costs)		
#	Weight measurement	Fluid balance recording (FBR)	Weight measurement	Fluid balance recording (FBR)	Total	Compared to Strategy 1	Compared to Strategy 3	Compared to Strategy 1	Compared to Strategy 3
1	None	No FBR	£0	£0	£0				
2	None	Partial FBR	£0	£160	£160	42		35	
3	Twice weekly	Partial FBR	£14	£160	£174	46		38	
4	Daily	Partial FBR	£41	£160	£201	53	7	44	6
5	Twice daily	Partial FBR	£81	£160	£241	64	18	53	15
6	None	Complete FBR	£0	£253	£253	67	21	56	17
7	Twice weekly	Complete FBR	£27	£253	£280	74	25	61	20
8	Daily	Complete FBR	£41	£253	£294	77	32	64	26
9	Twice daily	Complete FBR	£81	£253	£335 ^(b)	88	42	73	35

Table 7: Results of sensitivity analysis (3a) assuming longer duration of IV fluid administration

(a) IV fluids administered for 3 days (b) Difference due to rounding

Strategy		Cost over the duration of IV fluid administration ^(a) (£)			Number of extra co would have to be p patients to make s neutral	prevented per 1000	Number of extra complications that would have to be prevented per 1000 patients to make strategy cost neutral (including critical care costs)		
#	Weight measurement	Fluid balance recording (FBR)	Weight measurement	Fluid balance recording (FBR)	Total	Compared to Strategy 1	Compared to Strategy 3	Compared to Strategy 1	Compared to Strategy 3
1	None	No FBR	£0	£0	£0				
2	None	Partial FBR	£0	£53	£53	14		12	
3	Twice weekly	Partial FBR	£14 ^(b)	£53	£67	18		15	
4	Daily	Partial FBR	£14	£53	£67	18	0	15	0
5	Twice daily	Partial FBR	£27	£53	£80	21	4	18	3
6	None	Complete FBR	£0	£84	£84	22	5	19	4
7	Twice weekly	Complete FBR	£14 ^(b)	£84	£98	26	8	21	7
8	Daily	Complete FBR	£14	£84	£98	26	8	21	7
9	Twice daily	Complete FBR	£27	£84	£112 ^(c)	29	12	24	10

Table 8: Results of sensitivity analysis (3b) assuming shorter duration of IV fluid administration

(a) IV fluids administered for 1 day

(b) The cost of one-off weight measurement on admission is included in the twice weekly weight measurement strategies

(c) Difference due to rounding

M.4 Discussion

M.4.1 Summary of results

The cost associated with monitoring strategies varies according to the frequency of weight and fluid balance assessment and recording. The incremental cost difference is greatest in the comparison between Strategy 9 and no monitoring (Strategy 1) at £224 where Strategy 9 would need to avoid an additional 59 complications per 1000 patients to become cost neutral compared with Strategy 1 (49 if critical care costs are included). This increases to 100 per 1000 patients if a more conservative assumption is made about the time involved in completing fluid balance charts (83 if critical care costs are included).

Strategy 3 (current practice) would need to avoid 32 complications per 1000 patients to become cost neutral compared with Strategy 1 (26 if critical care costs are included). These numbers increase to 56 per 1000 patients if a more conservative assumption is made about the time involved in completing fluid balance charts (47 if critical care costs are included).

Under base case assumptions and compared with the lowest cost strategy (Strategy 1), Strategy 8 (daily weight measurement and complete FBR) would need to avoid 52 complications per 1000 patients to be cost neutral (43 if critical care cost is included). Compared to Strategy 3 (current practice), the number of additional complications that need to be avoided is 20 per 1000 patients (17 if critical care cost is included).

Using a more conservative assumption regarding the time involved in fluid balance recording, Strategy 8 would need to avoid 93 extra complications per 1000 patients to be cost neutral compared to Strategy 1 and 36 extra complications per 1000 patients to be cost neutral compared to current practice (Strategy 3). If shorter duration of IV fluid administration is assumed (1 day), the number of extra complications that need to be avoided falls to 26 complications per 1000 patients (21 if critical care costs are included) compared to the cheapest strategy (Strategy 1), and 8 complications per 1000 patients (7 if critical care cost is included) compared to current practice (Strategy 3). If longer duration of IV fluid administration is assumed (3 days), the numbers of extra complications that need to be avoided become 77 complications per 1000 patients (64 if critical care costs are included) when compared to the cheapest strategy (Strategy 1), and 32 complications per 1000 patients (26 if critical care cost is included) compared to current practice (Strategy 3).

M.4.2 Limitations and interpretation

The number of IV fluid therapy-related complications that each monitoring strategy can prevent and the proportion of patients who would require critical care because of these complications remain unclear from our review of the clinical evidence and further research is warranted. However, in a threshold analysis we estimated the number of major complications that would need to be prevented in order for monitoring strategies to be cost neutral or cost saving.

The GDG believed that this analysis gives a conservative estimate of the number of complications that need to be avoided for cost neutrality, as even if fewer major complications are prevented in practice compared to those estimated in our analysis, it is possible for a monitoring strategy to be cost effective if there are minor complications prevented as well or if the QALY gain associated with a major complication is large. To illustrate this, if we assume that preventing a complication is associated with only 0.2 QALY gain then it is necessary for Strategy 9 to avoid only 29 extra complications (26 if critical care cost is included) per 1000 patients to render it cost effective compared to no monitoring (Strategy 1) at a cost-effectiveness threshold of £20,000 per QALY

gained. Compared to current practice, the number of extra complications necessary to be avoided falls to 13 (12 when critical care is included) per 1000 patients to render it cost effective at a cost-effectiveness threshold of £20,000 per QALY gained.

For Strategy 8 (daily weight measurement and complete fluid balance recording) to be cost-effective compared to current practice (Strategy 3), at the same cost-effectiveness threshold, it is sufficient to avoid 10 extra complications per 1000 patients (9 if critical care cost is included).

The GDG thought that current monitoring and assessment was similar to Strategy 3 (weight measurement twice a week and partial fluid balance recording) in the general ward. If the introduction of a more rigorous monitoring strategy is able to reduce the incidence of fluid-related complications, then additional manpower costs could be justified. On this basis, once daily weight measurement and complete fluid balance recording (Strategy 8) could be justified.

The GDG also highlighted that the complication costs reported here may be underestimated as they do not include any staff time costs that maybe incurred during the investigation of any serious adverse events and consequent investigations. Hence, the numbers of complications that need to be averted are likely to be overestimated.

M.4.3 Conclusions

It was not possible to conduct a cost-effectiveness analysis of the different monitoring strategies given the lack of evidence of clinical effectiveness, however we conducted a threshold analysis to estimate the number of complications that a more frequent or thorough assessment would need to avert for it to be cost neutral compared to a less frequent assessment. Specifically, we compared strategies with a frequency of weight measurement from none to twice daily and a complete or partial fluid balance recording. According to the GDG's expert opinion, twice weekly weighing and partial fluid balance charting (only fluid inputs) is believed to be the most common practice in the NHS. The original analysis conducted showed that, under base case assumptions, the cost of current practice (Strategy 3) is £120 per patient over the duration of IV fluid administration, while the strategy with daily weight measurement and complete fluid balance recording (Strategy 8) costs £196.

This analysis indicated that, to be cost neutral compared to no weight measurement or fluid balance recording (Strategy 1), Strategy 8 would need to prevent 52 major complications per 1000 children, and compared to current practice (Strategy 3) it would need to prevent 20 major complications per 1000 children. This figure seemed plausible to the GDG as the analysis did not capture the possible health gain from the reduced number of complications. Sensitivity analyses were conducted where critical care cost was added to the cost of a major complication. This analysis showed that the number of extra complications to be averted, for cost neutrality, is reduced to 43 when compared to Strategy 1. When the time required for fluid chart completion was doubled, the number of extra complication of IV fluid administration also resulted in changing the number of extra complications that need to be averted compared to current practice to 28 and 8 per 1000 patients, respectively. The GDG concluded that daily weighing and complete fluid balance recording (including fluid inputs and outputs), represented by Strategy 8, could be justified in light of the costs and quality of life loss that are likely to result from any major complication.

The GDG believed that Strategy 9 (twice daily weighing and complete fluid balance recording) has increased costs with no further benefits compared to Strategy 8 (daily weighing and complete fluid balance recording). The GDG believed that the variation in weight within the same day may be due to other reasons and the healthcare professional may not change management based on a change in weight within the same day. Based on their collective experience, the GDG also considered additional benefits from complete fluid balance recording which may not be captured in this analysis and that

justifies recommending daily weighing and complete fluid balance recording (Strategy 8). However, the number of complications that each monitoring strategy can prevent and the proportion of patients who would require critical care because of intravenous fluid therapy related complications remain unclear from our evidence review and further research is required.

M.5 References

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