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Magnesium Sulfate Ready-to-Use Pack

Results of Field Evaluation

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Acronyms and abbreviations

FGD	focus group discussion
IDI	in-depth interview
IM	intramuscular
IV	intravenous
$MgSO_4$	magnesium sulfate
NEML	National Essential Medicines List
PE/E	preeclampsia and eclampsia
UNICEF	United Nations Children's Fund
WFI	water for injection
WHO	World Health Organization

1. Introduction

Preeclampsia and eclampsia (PE/E) are among the leading causes of maternal death and disability worldwide. The World Health Organization (WHO) estimates that PE/E account for at least 14% of maternal deaths in low-resource settings.[1] Over the years, different anticonvulsants have been used, including magnesium sulfate ($MgSO_4$), phenytoin, diazepam, and "lytic cocktail" (usually chlorpromazine, promethazine, and pethidine). Two randomized control trials, the Collaborative Eclampsia Trial for women with eclampsia and the $MgSO_4$ for Prevention of Eclampsia Trial for women with preeclampsia, provided the scientific evidence needed to promote $MgSO_4$ as the anticonvulsant of choice for the treatment of severe PE/E. In 2011, WHO developed evidence-based recommendations for the prevention and treatment of PE/E and recommended $MgSO_4$ as the preferred anticonvulsant in cases of severe PE/E. Most National Essential Medicines Lists (NEMLs) include $MgSO_4$ as the recommended anticonvulsant in cases of severe PE/E.

Despite its endorsement by WHO and its presence on most NEMLs, however, $MgSO_4$ is still underutilized, incorrectly administered, or unavailable at health care facilities in many low-resource settings, primarily due to the following barriers:

- The standard Zuspan and Pritchard regimens for $MgSO_4$ recommended by WHO are extremely complex and require intravenous (IV) and intramuscular (IM) administration; different dilutions for IV and IM doses; and different doses for IV, IM, loading, and maintenance (see Appendix 1). Most service providers will encounter eclampsia infrequently, and trying to remember the complex regimen is daunting.
- Multiple presentations of $MgSO_4$ (1%, 2%, 15%, 50%, etc.) are currently available on the market, making the calculation of dosing and dilution even more complex and confusing.
- The administration of calcium gluconate (the antidote for $MgSO_4$) is required in cases of respiratory distress due to magnesium toxicity, but there are frequent stockouts due to wastage from expiration.
- The IM administration of $MgSO_4$ requires 10mL of $MgSO_4$ plus 1mL of 2% lidocaine, which requires a syringe size that may not be routinely available in facilities.

As mentioned above, the major barriers are related to the current regimen. Manufacturer capacity to supply 50% $MgSO_4$ is not a significant issue. In 2012, PATH mapped the supply chain of $MgSO_4$ in order to understand the landscape of $MgSO_4$ manufacturers. To do this, we asked international procurement agencies (i+Solutions and the United Nations Children's Fund Copenhagen Supply Division) and the central medical stores in three countries (Bangladesh, Kenya, and Tanzania) about where they sourced $MgSO_4$. This landscape analysis identified 11 manufacturers of $MgSO_4$ currently supplying product to low-resource settings. Through other projects, we identified eight additional manufacturers that supply $MgSO_4$ for their domestic and/or international markets. Figure 1 shows where these 19 manufacturers are located, many of which produce 50% $MgSO_4$. Also, 5 of the 19 manufacturers operate in countries that are considered to have stringent regulatory authorities; therefore, quality of products from those countries should not be compromised.

A recent report estimates that the total addressable world market for $MgSO_4$ is 1,427,000 treatment cases (or women) if the incident rate of PE/E is estimated to be low (1%). This becomes 3,997,000 treatment cases (or women) if the incident rate is estimated to be high (2.8%). Of the total addressable world market, approximately half is estimated to currently have access to $MgSO_4$. Therefore, in the high-incidence scenario, the current market size is approximately 2 million treatment cases (or women), which has the potential to grow to approximately 4 million treatment cases (or women).[2] This market size can be sufficiently served by the existing $MgSO_4$ manufacturers. If the Pritchard regimen is used, approximately 5.5 million ampules will be required to cover about 2 million women in the high-incidence scenario (Table 1). This projected demand can be easily met, since, for example, one of the 19 manufacturers, Gland Pharma Limited (India), already has capacity to produce 150 million ampules (1mL to 10mL) per year.[3]

Figure 1. Locations of $MgSO_4$ manufacturers.

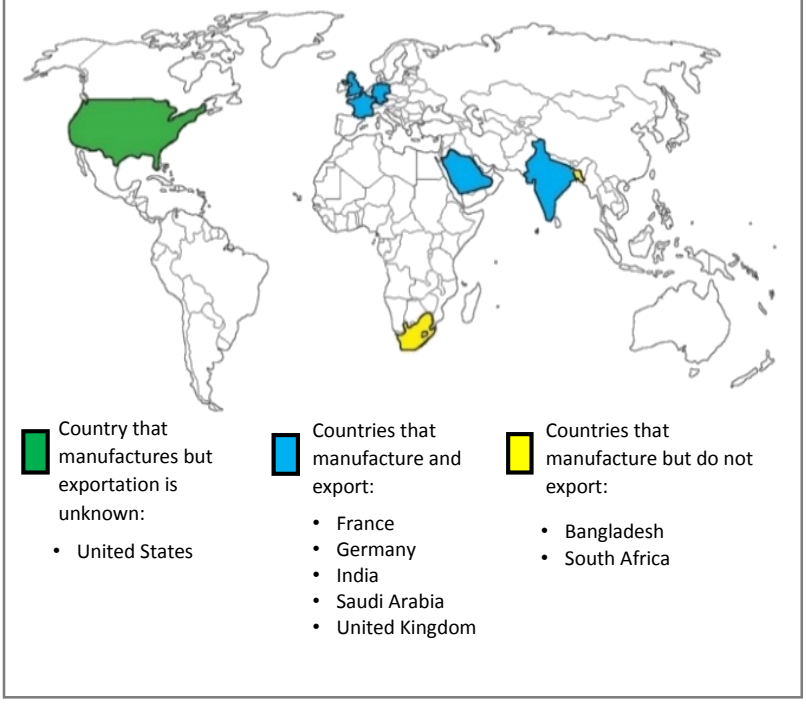


Table 1. Number of ampules required to cover the currently accessible market.[2]

	No. of ampules required per women	High-incidence scenario		Low-incidence scenario	
		Total currently accessible market (No. of women)	Total number of ampules required	Total currently accessible market (No. of women)	Total number of ampules required
Pritchard	8 x 5g/10mL (50%) ampules	1,914,000	15,312,000	683,000	5,464,000
Zuspan	6 x 5g/10mL (50%) ampules	1,914,000	11,484,000	683,000	4,098,000

However, there are only a few manufacturers of 20% $MgSO_4$ solution. Our Internet search yielded one manufacturer in Iran and one manufacturer in Italy that are producing a 20% $MgSO_4$ solution. Although the Dominican Republic, Ghana, Peru, and Senegal have all purchased 20% $MgSO_4$, the quality of the manufacturers and products is unknown.[4] Due to lack of availability of a 20% $MgSO_4$ from high-quality manufacturers, service providers in many countries are required to dilute a 50% solution at the time of use, which becomes a barrier for increasing usage of $MgSO_4$. One solution to this problem could be to entice qualified manufacturers that currently produce a 50% solution to make a 20% solution. However, given the unknown demand and the investments that manufacturers would need to make in production line adjustments and regulatory approvals, high-quality manufacturers might not be interested.

Accordingly, to reduce morbidity and mortality from PE/E, efforts should primarily focus on (1) increasing the usage rate of $MgSO_4$ and maximizing the demand size by alleviating fear of using $MgSO_4$ and by facilitating its ease of use; and (2) raising awareness about the importance of purchasing $MgSO_4$ from high-quality manufacturers. Thus, PATH has been working to reduce barriers to use of $MgSO_4$ and to increase its uptake. Our past and current activities include:

- Developed and conducted user evaluations of a mobile application job aid that assists providers in calculating the proper dosage and dilution of $MgSO_4$. These activities were carried out in Kenya in collaboration with the University of Washington, Seattle, USA.
- Hosted discussions with stakeholders and policymakers about simplifying the $MgSO_4$ administration regimen as a long-term solution.
- Developing a gel form of $MgSO_4$ that can be administered rectally.
- Evaluating the concept of a dilution bottle that has a pre-marked fill-line, which would obviate complex calculations at the time of use.
- Developing the Reusable, Electricity-Free, Low-Cost Infusion delivery system for $MgSO_4$.
- Developing the concept of ready-to-use packs to facilitate the ease of use of $MgSO_4$.

This paper is focusing on how we have been developing and defining the concept of ready-to-use packs.

2. Developing the concept of $MgSO_4$ ready-to-use packs

Appropriate strengths/doses of $MgSO_4$ solution are often unavailable at health care facilities. Most significantly, the lack of a readily available 20% $MgSO_4$ solution requires health care professionals to remember complex equations for diluting $MgSO_4$, and this has prevented wider use of $MgSO_4$ for treatment of PE/E. Other key supplies needed for administration of $MgSO_4$ also often are unavailable.

The ready-to-use packs we envisioned consist of a loading dose pack and a maintenance dose pack, each of which would contain the appropriate strength of $MgSO_4$. Other critical items, such as lidocaine and a 20mL syringe, could be added to these packs. A ready-to-use pack that contains the appropriate strength of $MgSO_4$ and other key supplies would obviate the need for dilution at time of use and could contribute to increased use of $MgSO_4$ for treatment of PE/E.

Although a lack of manufacturers capable of making a quality-assured 20% $MgSO_4$ solution could be a potential issue, this could be mitigated by working with international procurement organizations to consolidate demand for the ready-to-use packs, demonstrating sufficient demand, and then collaborating with credible manufacturers that are already manufacturing $MgSO_4$ of a different strength to produce a 20% $MgSO_4$ solution for those international procurement organizations.

In mid-2014, PATH conducted a rapid survey with stakeholders such as policymakers and health care professionals in four countries—the Democratic Republic of Congo, Ethiopia, Senegal, and Uganda—to understand current practices regarding the use of $MgSO_4$ for treatment of PE/E and stakeholders' perceptions about the concept of ready-to-use packs.[5] Findings from this survey indicated that there were challenges with the current administration regimen since it requires diluting 50% $MgSO_4$ to make a 20% solution. Also, stockouts of $MgSO_4$ and other items such as lidocaine and large syringes were found to be a significant issue. These findings support the need for ready-to-use packs. In fact, most respondents in

the rapid survey were enthusiastic about the concept of the ready-to-use pack and perceived that having the ready-to-use packs (both loading and maintenance dose packs) would be an advantage.

However, opinions varied significantly as to what additional items should be included in the packs; for example, what strengths and volume of $MgSO_4$ should be included in the loading dose pack and what additional items should be included in both the loading and maintenance dose packs. The number of items included in the packs would have significant impact on the cost per pack, space requirements for transport and storage, and distribution and inventory costs. In addition, should one of the items included in a pack be removed, the entire pack would have to be removed from inventory. Therefore, the more items that are included in a pack, the larger the risk of wastage will be. Our rapid survey was not able to explore how policymakers and health care professionals might respond to these potential tradeoffs or how they might decide what the optimal components should be for the loading and maintenance dose packs.

3. Defining the concept of the $MgSO_4$ ready-to-use pack

3.1 Objectives

As the next phase, we endeavored to ascertain what the optimal components of the ready-to-use packs should be. We also intended to elucidate users' willingness to use the packs as well as understand what potential impact the ready-to-use packs might have on country health systems.

We achieved these objectives through qualitative research methods: focus group discussions (FGDs) with health care professionals and in-depth interviews (IDIs) with experts (e.g., policymakers and procurement personnel) in Ethiopia and Uganda, where PE/E is a significant problem (see box below). Both countries utilize the Pritchard regimen; therefore, we were able to obtain sufficiently rich data as well as uncover some of the differences between the two countries.

PE/E in Ethiopia and Uganda

In Ethiopia, PE/E is reported as the second highest cause of maternal mortality; therefore, treating PE/E is a high priority for the government. The government of Ethiopia is committed to achieving Millennium Development Goal 5: Reduce maternal mortality. When the Ethiopian Midwives Association provided intensive basic emergency obstetric and newborn care training to 3,500 midwives and mid-level health professionals in most regions of the country, they included clear guidelines and protocol for administration of $MgSO_4$ and for the management of PE/E.

In Uganda, PE/E is seen as a significant public health challenge, which has not shown any sign of improvement over the past years. It currently accounts for 8% of the country's maternal deaths and is the fourth leading cause of maternal mortality after postpartum hemorrhage, puerperal sepsis, and obstructed labor. In Mulago Hospital, Kampala, the tertiary hospital in the country, a unit to exclusively treat PE/E was opened in September 2014.

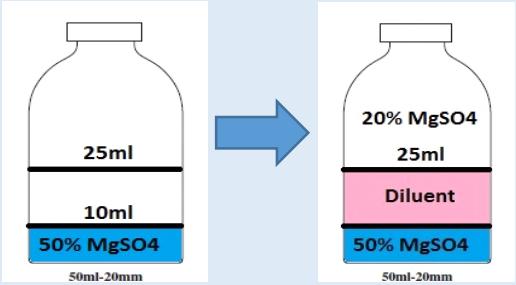
3.2 Methods

Based on the results of the rapid survey, we arrived at three possible configurations of ready-to-use packs (see Appendix 2), and then created mock-up packs using PATH's 3D printer. The mock-up packs were designed to visually demonstrate to FGD and IDI participants the items that could be included in the ready-to-use packs as well as the advantages and disadvantages of each pack configuration.

Pack option 1 included exact strengths of $MgSO_4$ solution: a 20% solution for IV injection and a 50% solution for IM injection. Two other mock-up packs included two types of dilution bottles on which PATH has been working: (1) pack option 2 included a dilution bottle that contained a 50% $MgSO_4$ solution; and (2) pack option 3 included a dilution bottle that contained water for injection (WFI) (see box below). The dilution bottles obviate the need to remember complex equations for dilution, thus minimizing the chance that the wrong dilution might be administered. Since these bottles can be provided as a component of the ready-to-use packs, we decided to evaluate the acceptability and feasibility of these dilution bottles by including them in the ready-to-use packs.

Dilution bottles

Pack option 2 included a dilution bottle that contained 10mL of 50% $MgSO_4$, and was pre-marked with a fill-line at 25mL. When a 20% $MgSO_4$ solution is required, a health care professional could simply add WFI to the bottle up to the pre-marked fill-line to make a 20% $MgSO_4$ solution. Then she/he could withdraw 20mL from the 25mL $MgSO_4$ solution for the IV loading dose. A small amount (5mL) of $MgSO_4$ would remain unused. (When a 50% $MgSO_4$ is required, the entire amount of the 50% solution could be withdrawn directly from the bottle for administration.)



Pack option 3 contained 12mL of WFI, and was pre-marked with a fill-line at 20mL. When 20% $MgSO_4$ solution is required, a health care professional could add the 50% $MgSO_4$ solution up to that fill-line (8mL of the 50% $MgSO_4$ solution) and then withdraw all of the resulting 20mL of solution from the bottle. Since 50% $MgSO_4$ solution is typically procured in 5g in 10mL ampule/vials, adding 8mL of 50% $MgSO_4$ to this dilution bottle would result in 2mL of unused 50% $MgSO_4$ solution being left in the ampule/vial.

In January 2015, FGDs and IDIs were held in Ethiopia and Uganda. Sample size in each country is described in the tables below.

Table 2. Focus group discussions.

Country	Location	Participant type	No. of FGDs	No. of participants
Ethiopia	Urban hospital (Addis Ababa)	Midwives	1	6
	Periurban hospital (Mekele)	Midwives	1	6
	Periurban hospital	Ob/Gyn	1	2
	Rural health center (Tigray)	Midwives	1	6
		Subtotal	**4**	**20**
Uganda	Urban (Kampala)	Midwives	1	8
	Urban	Ob/Gyn	1	8
	Periurban (Jinja)	Midwives	1	13
		Subtotal	**3**	**29**
		Total	**7**	**49**

Table 3. In-depth interviews.

Country	Decision-makers and procurement experts	No. of participants
Ethiopia	Ethiopian Midwives Association Pharmaceutical supply	2
Uganda	Ministry of Health senior officials Professor, Ob/Gyn Midwifery expert National Medical Stores Pharmacy	6
	Total	**8**

The Ministries of Health in both Ethiopia and Uganda identified regions of the country and higher-level facilities where $MgSO_4$ was in use. PATH country staff called health workers who used $MgSO_4$ to participate in FGDs and explained the purpose of the research. Those interested were invited to attend the FGDs where they were given a written consent form to ensure they understood the purpose of the study and had the opportunity to opt out.

FGDs in Ethiopia were held at health care facilities and at PATH's in-country office. All FGDs were facilitated by a PATH staff member experienced in qualitative research. FGDs were conducted in English and were recorded. When further clarification became necessary, the local language was used.

Participants were shown mock-ups of the three options for the ready-to-use packs, one at a time. In addition, a video that PATH developed was shown to demonstrate the use of dilution bottles included in pack options 2 and 3.

Midwives at FGD in Kampala, Uganda, watching a demonstration video created by PATH.

For data analyses, an outline of the key research themes was developed based on the topics shown in the discussion guides. All data were manually coded and assigned to the key themes.

3.3 Gaining a deeper understanding of the current situation

The FGDs and IDIs reaffirmed some of the challenges associated with the current regimen, with existing logistics and supply chain management, and with human resources in Ethiopia and Uganda. Although these challenges were not new to us, learning more about them helped us to gain additional insights.

The current regimen is especially challenging at lower-level health care facilities

The challenge of dilution from a 50% solution to a 20% solution for the IV loading dose was widely referred to as the most significant barrier to use of $MgSO_4$ due to its complexity. Serving a smaller population, lower-level health facilities have few cases of PE/E, which makes it more challenging for health care professionals at these levels to use the current regimen. Approximately 50 cases of PE/E are treated each month at Mulago Hospital, the largest tertiary hospital in Uganda, whereas one to two cases are treated every month at health centers. Since fewer cases of PE/E are treated at lower-level health care facilities:

- $MgSO_4$ solution is rarely used, and the unused solution often expires. Fewer units are then re-ordered, which results in more frequent stockouts.
- Midwives lose confidence in administering $MgSO_4$ even though they were trained to treat women with PE/E. As a result, they tend to either administer diazepam or IM injection of $MgSO_4$ only, which is considered to be easier to administer, and then refer patients to higher-level health care facilities. Alternatively, patients are referred, without treatment, to higher-level facilities.

  "…[when] it comes to calculations [and] dilutions, [midwives] don't have the confidence." [National-level expert, Uganda]

  "We don't dilute. We just give IM and refer [patients to hospital]." [Midwife, Uganda]

Moreover, the current regimen is time consuming for already overworked midwives. First, a loading dose is administered slowly over five minutes; subsequently, a maintenance dose is administered every four hours, if needed. A couple of experts commented that there are not enough staff at lower-level facilities and that the amount of time required to manage patients with PE/E is burdensome at these levels.

> *"In terms of human resources on the ground, there are only a few who can really monitor the woman after you have given [$MgSO_4$]."* [National Ob/Gyn expert]

"Necessary" items are not readily available, which presents additional challenges or results in substitution or non-treatment

Necessary items, such as $MgSO_4$ solution, 20mL syringes, lidocaine, and WFI, are often out of stock or are not in the correct format. Consequently, health care professionals are forced to use alternatives or even to forego treating women at their facilities.

In Uganda, when a woman with PE/E comes to a Health Center II facility, which does not have a midwife, she is referred to a midwife at a small, private facility, even though $MgSO_4$ is rarely available at private facilities. Although Mama Kits, which include $MgSO_4$, are distributed to lower-level health care facilities, several experts noted that sufficient quantities of the kits are often unavailable.

- The National Medical Store in Uganda purchases $MgSO_4$ in 2.5g in 5mL ampules. Not only is this more expensive than purchasing $MgSO_4$ in 5g in 10mL ampules, it makes the calculation of a 20% dilution more complicated.

- 20mL syringes—the ones most appropriate for administration of $MgSO_4$ via IV and IM—are procured in insufficient quantities in both countries. The lack of 20mL syringes presents additional complications for the IV loading dose. If health care workers have only 10mL or 5mL syringes, they will need four 5mL syringes or two 10mL syringes for IV loading doses. As a result, they have to figure out how much WFI and 50% solution should be withdrawn into each 5mL or 10mL syringe in order to make a 20% $MgSO_4$ solution.
- Due to the lack of 20mL syringes, a 10mL syringe is commonly used to provide the entire 11mL of solution (10mL of 50% $MgSO_4$ solution plus 1mL of 2% lidocaine) for IM injections. Most respondents said that there is sufficient space at the end of the 10mL syringe to accommodate an extra 1mL of lidocaine. As a result, the amount of solution is an approximation in almost all cases. When a 10mL syringe is not available, two 5mL syringes are used.
- WFI is procured in 10mL vials in both countries (in Ethiopia, IV bags of saline are also used for making dilutions). Since 12mL of WFI is needed to make 20% $MgSO_4$ solution (from 5g in 10mL $MgSO_4$ solution), two 10mL WFI vials are then used, thus 8mL of WFI is wasted. Regardless, few experts were concerned about wastage of WFI since they believe that such wastage is infrequent.

Midwives in a rural health center in Tigray, Ethiopia, discussing $MgSO_4$ ready-to-use packs.

3.4 Key findings

Key finding 1: Overall, the ready-to-use packs were well accepted; however, focus groups and experts considered 20% $MgSO_4$ solution as the most crucial item

In general, the concept of a ready-to-use pack was well accepted. FGD participants and experts said that any of the three pack options would be an improvement over current practices (refer to Appendix 3 for detailed feedback on each option). Almost all focus groups and many experts agreed that they would use the packs or recommend packs for use. They believed that the packs would lead to improved treatment.

> *"Even if it costs a bit more, it can't be compared to a woman being referred. A health worker can't [administer $MgSO_4$], and they die!"* [Ministry of Health decision-maker, Uganda]

> *"[The ready-to-use pack] avoids confusion; women will receive the right dosage and the right treatment with the right protocol easily…."* [National expert, Ethiopia]

A key reason stated was the convenience of having all necessary components included in one package. Especially in emergencies, such as severe eclampsia, it is critically important that the necessary components are readily available in the correct strength/dose. Since stockouts of items necessary for treating PE/E are a major issue, focus group participants and experts appreciated having all necessary components in one pack.

> *"It is simple. I won't have any fear…."* [Midwife, Uganda]

However, after further discussion with participants, we discovered that their preference for the ready-to-use packs actually boiled down to desire to have two items included in the packs that they currently do not have: 20% $MgSO_4$ solution and lidocaine. Solution of 20% $MgSO_4$ is not currently being procured. Lidocaine is procured in both countries, but only in multi-dose vials (100mL and 20mL vials in Ethiopia

and Uganda, respectively), because lidocaine has a variety of indications for use. When multi-dose vials are used, there is a risk of contamination, since lidocaine is drawn into the syringe after the magnesium sulfate. Moreover, many people emphasized that including a 20% $MgSO_4$ solution in the loading dose pack would be the key to addressing the dilution problem and would significantly alter the current practices of either withholding treatment or giving incorrect treatment.

> *"We have lost mothers who have received 50 percent [solution] via IV without dilution…. So this is something much deeper than you can imagine…. The consequences of this 20 percent solution is likely to be much more efficient than we can even imagine…."* [Ob/Gyn, Uganda]

Since having a 20% $MgSO_4$ solution is crucial, all focus groups and experts selected option 1 as their most preferred pack. On the contrary, many focus groups and experts chose option 2 as their least preferred option due to the complexity of using the dilution bottle, discussed in detail further on. Only one expert selected option 2 as his most preferred option, under the assumption that it would simplify procurement practices and be less expensive.

Key finding 2: Opinions varied as to what other items should be included in the packs

Even though participants expressed a clear preference for including a 20% $MgSO_4$ solution and lidocaine in the pack, opinions varied significantly as to what other items should be included. This might be because some participants and interviewees focused solely on convenience and failed to recognize that items that they had mentioned are typically already available at their health care facilities, are rarely needed, or are impractical to be included.

- ***Adding syringes:*** A few experts emphasized the importance of including 20mL syringes, and a few focus groups stressed the importance of including 10mL syringes (for IM) and 20ml syringes (for IV). A few focus groups even suggested including a "magnesium sulfate syringe"—a 15mL syringe specifically for use in treating PE/E.
- ***Adding an additional 2g in 10mL $MgSO_4$ solution:*** A few suggested including an additional 2g in 10mL $MgSO_4$ solution, since it is needed for supplemental doses if convulsions continue after the loading dose (Ethiopia). However, it is not clear how often women experience persistent convulsions following the loading dose.
- ***Adding other medical supplies:*** A few focus groups suggested including medical supplies such as a catheter, urine bag, cannula, and 18-gauge needle. A few experts indicated that instructions or wall-charts should be included in the packs.
- ***Adding calcium gluconate:*** There was a split among focus groups regarding whether calcium gluconate should be included in the pack. Some said it would be important to include it, while others suggested it should be available at the facility but not included in the pack. Almost all experts recommended making calcium gluconate available at facilities but not including it in the packs, considering that it is needed only on rare occasions.

Key finding 3: No consensus was gained on how many doses should be included in the maintenance pack, potentially due to lack of understanding about the protocol for maintenance doses

We presented focus groups and experts with a mock-up maintenance dose pack that contained items required for one dose: one ampule/dilution vial of 50% $MgSO_4$, one ampule of lidocaine, and one 20mL syringe. We thought that health care professionals could use the necessary quantity of packs in accordance with the number of maintenance doses their patients might require. However, the majority of

focus groups and experts in both countries preferred inclusion of six doses in a single maintenance pack, stating the convenience of having all necessary items in one pack.

We countered that if a patient required fewer than six doses, the pack might end up with unused doses. In response to this, a few focus groups and experts said they could save the unused doses for other patients. A few other focus groups indicated that if all six doses were available in one pack, they would give all of them to one patient. The difference in responses might be because FGD participants and experts were not clear about the approved protocol for maintenance dosing. In fact, midwives who participated in the FGDs stated they were unclear as to when to stop administering $MgSO_4$ maintenance doses.

Key finding 4: Ready-to-use packs might add cost and complexity

Several major concerns were raised about the ready-to-use packs:

- ***Incomplete/partial packs.*** Some of the pack components might be removed for different purposes or might expire earlier than other components, which would result in incomplete/partial packs. The ready-to-use packs would include items that have multiple uses (e.g., syringes, lidocaine), which might be taken from the packs and used for different purposes. In Uganda, a few groups admitted they would take components from a pack in case of an emergency or stockout. Accordingly, one expert in Uganda even questioned the validity of the ready-to-use pack.

  "If something is out of stock because of budget [constraint]…, then someone would naturally raid the packs. Therefore, the very premise…of a pack has got to be questioned as well." [National procurement expert, Uganda]

  In addition, the expiration date of each component might differ; therefore, the expiration of the packs would need to be established based on the earliest expiration date of any component. This means that some of the components could still be valid (i.e., within their expiration date) when the pack itself expires. A few focus groups and experts said they would discard the pack if the pack reached the stated expiration date; however, some focus groups and a few other experts said they would discard only the expired components and use the remainder of the pack. If only the expired items in the pack were discarded, this would create an incomplete/partial pack, again calling into question the rationale for having a ready-to-use pack.

- ***Cost.*** Almost all components that would be included in the ready-to-use pack are currently and readily available. Some focus groups and experts, therefore, were concerned that packaging already available items in a single pack might add cost. However, one participant countered that cost should be weighed against the impacts of an improved presentation.

  "I don't think cost should be a key thing if we have such a very good package…because it will save many more mothers." [Ob/Gyn, Uganda]

- ***Added complexity within procurement processes.*** A few procurement experts expressed concern that the ready-to-use packs would add complexity to their current procurement processes. In Uganda, the National Medical Stores would need to unpack the ready-to-use packs and register each item in their tracking system. In addition, a few procurement experts questioned the amount of storage space that the ready-to-use packs would require, compared to that required for storing individual items.

Key finding 5: Dilution bottles were perceived as being only a slight improvement over current practices

Two different dilution bottles were evaluated as part of the ready-to-use packs. Although the two options that included dilution bottles were considered to be improvements over current practices, the bottles themselves were viewed as not offering a significant benefit for the following reasons:

Midwife in Tigray with the dilution bottle included in pack option 2.

- Multiple steps still would be required for dilution, and these steps were regarded as being as complex and time consuming as current practices.

  "[The dilution bottle] needs extra preparation and even still it's not straightforward for the midwives to do it." [National-level decision-maker, Ethiopia]

- Both types of dilution bottles would end up with some unused amount, and focus group participants and experts were concerned about the wastage.
- A few people expressed concern that some health care workers might mistakenly withdraw the wrong amount or mistakenly administer the unused amount of $MgSO_4$ in the dilution bottle to another patient later on.
- Some thought that people might overfill the dilution bottle even with the pre-marked fill-line. One Ob/Gyn mentioned that having the fill-line would encourage health care professionals to automatically fill the bottle with diluent, instead of deliberately diluting $MgSO_4$. This might, in turn, result in careless mistakes.
- In Uganda, health care workers know to administer 14g of $MgSO_4$ for women with PE/E (4g for IV and 10g for IM injections). Therefore, diluting 10mL of 50% $MgSO_4$ solution to make 25mL of 20% solution would not be intuitive for them.

Only procurement personnel made positive comments about the dilution bottle. They liked pack option 2 with the dilution bottle because only one type of bottle would need to be procured for both the loading and maintenance doses and for both IV and IM injections. This would reduce complexity in procurement and supply chain management.

4. Conclusion

The FGDs and IDIs reaffirmed two key challenges. The primary challenge is associated with the current regimen: diluting a 50% $MgSO_4$ solution to make a 20% solution. This challenge, though raised at all facility levels, is more significant at lower-level health care facilities, which deal with only a few cases of PE/E per month and suffer from staff shortages. At these lower levels, midwives, even though they are trained to manage PE/E, lose confidence in administering $MgSO_4$ since they rarely use it and do not remember the complex administration regimen and calculation required to dilute 50% $MgSO_4$ solution. They end up referring patients to higher-level health care facilities. Even if they manage to treat PE/E, the current regimen demands time and effort, which creates an additional burden for the already overworked midwives.

The other key challenge is frequent stockouts of necessary items. This either requires health care professionals to use alternative items, or, most unfortunately, results in non-treatment. Stockouts of

necessary items are also more significant at lower-level health care facilities, since they are not replenished in a timely manner.

All these challenges point to the importance of improving supply chains and having a 20% solution available, as well as the importance of developing effective technology solutions that can make administration of $MgSO_4$ easier and simpler, especially at lower-level health care facilities.

Ready-to-use pack

Overall, the concept of a ready-to-use pack was well accepted. Stakeholders stated that any of the options we presented would be an improvement over current practices.

However, the reason expressed for wanting the ready-to-use pack was the convenience of having all necessary items included in a single package. When we asked about components preferred for inclusion in the pack, the strongest consensus from virtually all participants was for a 20% $MgSO_4$ solution and an individual dose of lidocaine; opinions about all other components varied. Most significantly, a number of the participants underscored the fact that including a 20% solution in the pack would be the key to addressing the existing problems with dilution, and that this would significantly contribute to reducing non-treatment or incorrect administration of $MgSO_4$.

Some FGD participants and experts questioned the validity of a ready-to-use pack. They were concerned about the overall cost of the packs, that some components of the pack might have shorter expiration dating than other components, and that packs might be opened and components taken for other purposes. Procurement personnel also expressed concern that the ready-to-use packs would add complexity to their current procurement processes. In Uganda, the National Medical Stores would be required to open the packs and register each item contained in them. Additional storage space would also be required for the packs, compared to that required to store the individual items.

Dilution bottle

Two different dilution bottles were evaluated as a potential component of the ready-to-use pack. Although the two options that included dilution bottles were considered to be improvements over current practices, the dilution bottles themselves were determined to not offer much benefit: (1) they would require steps just as complex and time consuming as current practices; (2) unused solution would remain, which would be wasted or could result in error if someone used the remainder later on or mistakenly withdrew the wrong amount; (3) the fill-line might not be effective enough to prevent overfill or might encourage health care professionals to add diluent to the line without measuring; and (4) in Uganda, diluting 10mL of 50% $MgSO_4$ would not be intuitive since this method is different from the one currently used by health care professionals.

5. Recommendations

We recommend **not** pursuing a $MgSO_4$ ready-to-use pack or a dilution bottle. Instead, efforts should be directed toward increasing the availability of a quality-assured 20% $MgSO_4$ solution in low- and middle-income countries. Currently, there are only a few manufacturers of a 20% $MgSO_4$ solution. Although the Dominican Republic, Ghana, Peru, and Senegal have each purchased 20% $MgSO_4$, the quality of the manufacturers and the $MgSO_4$ are unknown.

However, high-quality manufacturers might not be interested in producing a 20% $MgSO_4$ solution due to the unknown demand and the investments they would need to make in production line adjustments and regulatory approvals. In order to incentivize high-quality manufacturers to produce a 20% $MgSO_4$ solution, a three-prong approach would be required: (1) articulate demand by estimating demand size; (2) assure demand through proper forecasting and procurement planning at the country level; and (3) consolidate demand by working with international procurement agencies, thus reducing the market entry costs for manufacturers.

Since the challenges with the current regimen are most significant at lower-level health care facilities, additional effort should be made to increase and ensure the proper use of $MgSO_4$ at those facilities. PATH's work in developing the Reusable, Electricity-Free, Low-Cost Infusion delivery system as well as a gel form of $MgSO_4$ for rectal administration should be the areas of focus in this regard. These new technologies would make it easier for health care professionals at lower-level facilities to administer $MgSO_4$, thereby increasing proper use of the product. Efforts to develop new technology solutions should also be combined with continued efforts to train midwives on proper use of $MgSO_4$, as well as continued work on improving delivery of the product to lower-level facilities through better forecasting, procurement planning, and logistics.

References

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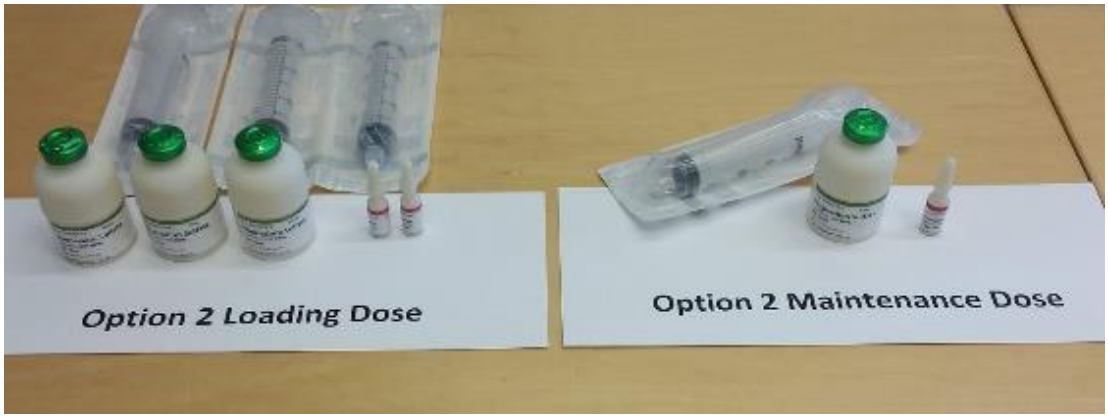
Appendix 1. Prichard versus Zuspan regimen

	Loading dose	Maintenance dose
Prichard regimen	4g $MgSO_4$ in 20mL water for injection (20% solution) is given intravenously over 3 to 5 minutes, followed immediately by 5g $MgSO_4$ in 10mL water for injection (50% solution) given through deep intramuscular (IM) injection into each buttock (a total of 10g). If convulsion persists over 15 minutes, 2g $MgSO_4$ in 10mL water for injection (20% solution) is given over 2 minutes.	5g $MgSO_4$ in 10mL water for injection (50% solution) is given through IM injection every 4 hours alternately on each buttock until 24 hours after delivery or after the last convulsion, whichever is later.
Zuspan regimen	4g $MgSO_4$ diluted with 100mL fluid is given intravenously over 5 to 10 minutes.	1g $MgSO_4$ is given through IM injection every hour until 24 hours after delivery or after the last convulsion.

Appendix 2. Configurations of the ready-to-use-packs

Option 1:		
	Loading dose pack	Maintenance dose pack
Item	**Quantity (primary container)**	**Quantity (primary container)**
Magnesium sulfate: 4g in 20mL (20%)	1 ampule	---
Magnesium sulfate: 5g in 10mL (50%)	2 ampules	1 ampule
Lidocaine: 20mg in 1mL (2%)	2 ampules	1 ampule
Syringe 20mL	3	1

Option 2:		
	Loading dose pack	Maintenance dose pack
Item	**Quantity (primary container)**	**Quantity (primary container)**
Magnesium sulfate: 4g in 20mL (20%)	---	---
Magnesium sulfate: 5g in 10mL (50%)	3 dilution bottles	1 dilution bottle
Lidocaine: 20mg in 1mL (2%)	2 ampules	1 ampule
Syringe 20mL	3	1



Option 3:		
	Loading dose pack	Maintenance dose pack
Item	**Quantity (primary container)**	**Quantity (primary container)**
Water for injection: 12mL	1 dilution bottle	
Magnesium sulfate: 4g in 20mL (20%)	---	---
Magnesium sulfate: 5g in 10mL (50%)	3 ampules	1 ampule
Lidocaine: 20mg in 1mL (2%)	2 ampules	1 ampule
Syringe 20mL	3	1

Appendix 3: Feedback on Ready-to-Use Pack Options

Pack	Benefits	Challenges	Suggestions

Option 1: Most preferred overall	• Overwhelming support for this option since it includes a 20% solution of $MgSO_4$ in a 20mL ampule for the intravenous (IV) loading dose. Major reasons:
	  ◦ Would eliminate the need for dilution, resulting in easier administration, reduced workload, reduced risk of contamination, fewer mistakes (fewer occurrences of withholding treatment of women when needed), increased confidence of midwives.
	  ◦ Additional benefits: time savings, elimination of wastage. Some also pointed out the benefit of having few components in a pack, since there would be less concern about expiry of the pack.
		• Very minimal concerns, including potential for increased cost, midwives mistakenly using insufficient amount.
		• Potential challenge: increased complexity in procurement and distribution systems since a 20% $MgSO_4$ solution would have to be registered, in addition to the 50% solution, which has already been registered.
			• A few groups suggested using colors to differentiate the 20% and 50% solutions and using a vial instead of an ampule for the 20% solution.
			• Experts in Ethiopia suggested providing a 20% solution of $MgSO_4$ separately in a larger volume, rather than creating a pack.

Option 2: Least preferred overall	• Almost all focus groups and some experts identified pack option 2 as an improvement over current practices because of the dilution bottle:
	  ◦ Diluting 50% solution within the bottle would be easier than current practices.
	  ◦ The fill-line would provide confidence, since it would validate that dilution was done properly.
	  ◦ The need for only one dilution bottle for both the loading and maintenance doses would be cost effective and reduce complexity.
	  ◦ Would ensure that the solution is well mixed.
	• Another reason for preferring this option was that bottles would be less likely to break than ampules.
		• Some focus groups and experts indicated that option 2 is not much better than current practices because:
		  ◦ Time required and complexity of diluting would remain the same.
		  ◦ Stockouts of water for injection (WFI) would remain a concern since WFI would not be included in the pack.
		  ◦ Possible risk of contamination with the flip top.
		• With regard to requiring users to withdraw 20mL from 25mL of diluted 20% $MgSO_4$ solution:
		  ◦ Almost all groups and some experts identified wastage as a concern.
		  ◦ A few stated that it would be confusing, and there would be the risk of using the remainder later or drawing the wrong amount.
		• Having 5g in 10mL in the loading dose would be confusing. In Uganda, service providers know to use 14g of $MgSO_4$ (4g for IV injection and 10 for intramuscular injection). Having 5g in 10mL for the
			• A few groups suggested including WFI and a tool to open the cap in the pack.

Pack	Benefits	Challenges	Suggestions
		option 2 IV loading dose and diluting it to make a 25mL solution would not be intuitive. • One Ob/Gyn expressed concern about the fill-line, since it would encourage automatic dilution and prevent people from "thinking" to ensure correct dilution.	
Option 3: Second overall	• Many focus group participants and some experts identified the inclusion of WFI as a benefit, although WFI is readily available. • Some groups identified that there would be less wastage compared with option 2 and current practices. • A few groups and experts indicated that: o The fill-line would be helpful. o Dilution with this option would be easier than with option 2 and using current practices. o This option would ensure that the solution is well mixed. o This option is similar to current practices.	• Some focus groups and a few experts identified that there would still be wastage (2mL of $MgSO_4$) with this option. • Some experts did not see a significant improvement with this option since it would require extra preparation and the process would not be straightforward for midwives. Some FGDs said training would be needed. • A few groups and experts expressed concern about cost. • One expert shared concern that this option would add complexity to procurement processes since single-use WFI would have to be registered. • A few worried about risk of over-filling the bottle and giving the wrong dose.	• None.