



## **FAST RCT PROTOCOLS**

# **Prospective Randomized Clinical Trial of Fetal Atrial Flutter & Supraventricular Tachycardia Therapy**

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**Study Funded by:** The Canadian Institutes of Health Research (CIHR)

**PROTOCOL AGREEMENT**

I have read the protocol specified below. In my capacity as Qualified or Principal Investigator (QI/PI), my duties include ensuring the safety of the study subjects enrolled in Randomized Clinical Trials under my supervision and providing the Sponsor Dr. Edgar Jaeggi at The Hospital for Sick Children, Toronto, Canada, with complete and timely information, as outlined in the protocol. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted Good Clinical Practice (GCP) principles and to abide by the terms of this protocol.

REB number(s) at your site: \_\_\_\_\_

Protocol Title: FAST Therapy Trial (indicate which study or studies)

- RCT Sub-study A: Fetal Atrial Flutter *without* Hydrops
- RCT Sub-study B: Supraventricular Tachycardia *without* Hydrops
- RCT Sub-study C: Supraventricular Tachycardia *with* Hydrops

Protocol Version/Date: \_\_\_\_\_

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*Site/Study PI Signature* *Date*

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*Name and Title (Print)*

*Site #* \_\_\_\_\_

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## **LIST OF ABBREVIATIONS**

AE: Adverse event

AF: Atrial flutter

AET: Atrial ectopic tachycardia

AV: Atrioventricular

AVRT: AV reentrant tachycardia

BID: Twice a day

BP: Blood pressure

Bpm: Beats per minute

CRFs: Case report forms

DSMB: Data & Safety Monitoring Board

ECG: Electrocardiogram

ECHO: Echocardiography

F/M: Fetal/maternal

HR: Heart rate

IUD: Intrauterine demise

NND: Neonatal death

PJRT: Permanent junctional reciprocating tachycardia RCT: Randomized Clinical Trial

REB: Research Ethics Board

SAE: Serious adverse event

SAR: Serious adverse reaction

SUADR: Serious Unexpected Adverse Drug Reaction

SVA: Supraventricular tachyarrhythmia

SVT: Supraventricular tachycardia

TID: Three times a day

WPW syndrome: Wolff-Parkinson-White syndrome

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## 1. INTRODUCTION

Although fetal supraventricular tachyarrhythmias (SVAs), including atrial flutter (AF) and other forms of supraventricular tachycardia (SVT), are the most common causes of intended in-utero fetal therapy, none of the drugs used has ever been evaluated for their effects on the mother and her child in a Randomized Clinical Trial (RCT). In the absence of such evidence, there is no consensus for the optimal management. The *Fetal Atrial Flutter and Supraventricular Tachycardia (FAST) Therapy Trial* is a prospective multi-centered trial that addresses this knowledge gap to guide future fetal SVA therapy to the best of care.

Study components of the FAST Therapy Trial include:

- **Three prospective RCT sub-studies (FAST RCT)** to determine the efficacy and safety of specific transplacental drug regimens in suppressing fetal AF without hydrops, SVT without hydrops, and SVT with hydrops. Additional information on the RCT sub-studies is available at ClinicalTrials.gov under listing #NCT02624765. Participation in the regulated FAST RCTs is currently restricted to pre-selected centers.

**A prospective observational cohort study (FAST Registry)** is a non-regulated Registry which seeks to establish an international database of fetal SVA management done to date, to be used to publish information on the results of current prenatal care and to evaluate the need for additional FAST RCTs. Participation in FAST Registry requires site REB approval and an executed legal contract with the Hospital for Sick Children, Toronto (REB Number# 1000048953).

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This protocol applies to centers that are participating in the RCT sub-studies.

The **primary outcome** of the FAST RCT will be the proportion of term deliveries of live-born children with a normal cardiac rhythm. Term delivery is defined as birth 37 0/7 weeks gestation or later.<sup>3,4</sup> **Secondary outcomes** will determine the efficacy of 1<sup>st</sup> line, 2<sup>nd</sup> line, 3<sup>rd</sup> line, and maintenance drug therapy in controlling the different arrhythmias prior to birth and patient safety. We expect faster cardioversion to be significantly associated with higher rates of normal term deliveries and less perinatal mortality, morbidity and resource utilization due to shorter hospitalization.

## 2. STUDY BACKGROUND AND RATIONALE

**2.1 CLINICAL RELEVANCE OF SVA.** SVA is the most common cause of fetal tachycardia  $\geq 180$  bpm, affecting 1/4,000 pregnancies. Despite its relative rarity, it is a *leading cause of fetal heart failure, prematurity and perinatal death*. The development of fetal hydrops (defined by >1 of these symptoms: abdominal, pleural, pericardial effusion(s); skin edema) is associated with *perinatal mortality as high as 35%*. The risk of hydrops increases if SVA presents at a younger gestational age and is rapid and enduring, but even intermittent SVA may

have serious consequences.<sup>5,6</sup> In the largest retrospective study to date on fetal SVA by Jaeggi et al, 40% of 114 fetuses with SVT presented with hydrops, which was associated with a perinatal mortality rate of 21%.<sup>1</sup> In another study by Simpson et al, fetal hydrops occurred in 41% of 127 SVA cases and was associated with 27% mortality.<sup>5</sup> In the absence of fetal hydrops, the risk of SVA-related perinatal mortality is much lower (0%-4%).<sup>1,5</sup>

**2.2 MECHANISMS OF SVA.** The main mechanisms of fetal SVA, AF and SVT, may be distinguished by echocardiography.<sup>7,8</sup> Their prenatal differentiation is clinically relevant since *AF is associated with a lower conversion rate to sinus rhythm in response to antiarrhythmic drug therapy compared with SVT.*<sup>1</sup> AF is sustained by a circular macro-reentrant pathway within the atrial wall and the AV node is not part of the reentry circuit.<sup>9</sup> Typical atrial rates range between 400 and 500 bpm, which is most commonly associated with 2:1 AV conduction and ventricular rates between 200-250 bpm. The atrial rate in SVT is almost always <300 bpm. Fetal SVT itself is produced by 3 main mechanisms: 1) AV reentrant tachycardia (AVRT), involving the AV node for antegrade (AV) conduction and a fast retrograde (VA) conducting accessory pathway; 2) permanent junctional reciprocating tachycardia (PJRT), like AVRT but with slow retrograde pathway conduction; and 3) atrial ectopic tachycardia (AET) due to an atrial focus with enhanced automaticity. The differentiation of AVRT, PJRT or AET by fetal echocardiography can be difficult and will not be required for the RCT since there is no evidence that it affects the result of therapy. In addition, AVRT (60%) and AF (30%) account for 90% of all fetal SVA cases.<sup>1</sup> Rare cases with SVT and AF will be classified in FAST according to the main mechanism at the 1<sup>st</sup> exam.<sup>9</sup>

**2.3 MANAGEMENT AND OUTCOME OF FETAL SVA.** Management options upon a new diagnosis of fetal SVA include observation, drug therapy, and delivery with postnatal cardioversion. Care decisions are largely influenced by SVA characteristics, gestational age, fetal-maternal health, and willingness of the mother to undergo treatment. *Close observation* without drug therapy is usually a safe approach for the fetus with infrequent, brief SVA episodes, as heart failure will rarely develop. Conversely, fetuses with incessant SVA tend to develop fetal hydrops if left in tachycardia. Prior to 37 weeks, *transplacental pharmacological treatment* to obtain a normal rhythm is the preferred option because the hazard associated with preterm delivery outweighs the risks of drug therapy. After 37 0/7 weeks, *primary delivery by caesarean section* is often elected. Cardioversion prior to birth will also facilitate *vaginal delivery* by allowing the interpretation of the fetal heart rate tracings during labor. In the study by Jaeggi<sup>1</sup>, 15% of mothers did not receive prenatal treatment because the arrhythmia was considered insignificant, 15% were immediately delivered for postnatal cardioversion, and 70% received transplacental drug therapy. Still, preterm delivery was a frequent outcome of treated cases (37%) due to failure of the elected drug to rapidly control the fetal SVA. Newborns with SVT typically receive antiarrhythmic drug therapy during the 1<sup>st</sup> year, while AF is expected to not recur.<sup>9</sup>

Optimizing the management to improve outcomes of fetal SVA is a major research focus of the FAST Therapy Trial. Unnecessary interventions and complications could be prevented with the primary use of the most efficient therapy for fetal SVA. Based on published data, the preterm birth rate should be no higher than 7.6%.<sup>10,11</sup> With an incidence of 37% preterm deliveries in Jaeggi's study,<sup>1</sup> fetal SVA was associated with 5-fold increased odds of prematurity. Preterm infants are at substantially greater risks for mortality and morbidity than term infants due to immaturity-related complications, including respiratory distress syndromes (7.5 fold increased risk e.g. at 37 vs. ≥38 weeks).<sup>12</sup> The neonatal need of intensive care and length of hospital stay are inversely related to the

gestational age at birth.<sup>11, 13</sup> Neonatal mortality in babies born between 34-38 weeks is 4.6 times higher than in term infants.<sup>14</sup> In addition, compared with term babies, delivery <38 weeks is associated with poorer developmental and educational outcomes, and increased burden of later disease.<sup>11, 15, 16</sup> Finally, delivery by caesarean section is associated with a substantial list of maternal risks, with correlations that typically favor vaginal delivery, including shorter hospital stays, less maternal morbidity, lower costs, and lower risks for adverse obstetric and perinatal outcomes for next births.<sup>11, 17</sup>

**2.4 TRANSPLACENTAL THERAPY OF SVA.** The rationale to offer transplacental drug therapy to mothers with fetal SVA is to achieve rapid and lasting cardioversion, to prevent or treat fetal heart failure, and to allow the pregnancy to continue to term with the delivery of a healthy child. Transplacental fetal therapy generally occurs with one of three 1<sup>st</sup> line agents, digoxin, flecainide, and sotalol, which all have been used for decades to treat fetal SVA. Amiodarone or direct fetal drug administration are mainly reserved for therapy-resistant SVA because of increased risks of maternal and fetal adverse events (AEs).<sup>5-9, 18-31</sup> Detailed descriptions of drug actions and possible AEs related to the use of the study drugs are provided in the *Monographs*. In brief:

- **DIGOXIN** actions include parasympathetic slowing of sinus node and prolongation of the AV nodal refractoriness. In the absence of hydrops, oral digoxin is well absorbed and transferred to the fetus, to reach fetal serum concentrations that are close to those in maternal serum (F/M ratio 0.8-1) within 3-5 days.<sup>2</sup> No serious AEs (SAEs) have been reported, but nausea, anorexia, headache, visual disturbances and dizziness are among the more common patient complaints.<sup>1</sup>
- **FLECAINIDE** inhibits Na<sup>+</sup> channels, slowing conduction and increasing refractoriness of all cardiac tissues. Flecainide is well-absorbed and transferred to the fetus to reach therapeutic levels within 3 days (F/M ratio 0.7-0.9).<sup>2, 32</sup> At maternal serum concentrations >1 mcg/ml, the QRS interval may prolong and the risk of proarrhythmia increase. Infrequent maternal AEs include blurred vision, nausea, constipation, dizziness, and headache. Maternal SAEs have not been reported but there is one case of unexplained in-utero demise of a non-hydropic fetus 23 years ago.<sup>6</sup>
- **SOTALOL** is both an iKr channel and β-blocker, with β-blockade as the main effect at doses <160 mg/day. The combined effects decrease heart rate, and prolong action potential duration and tissue refractoriness throughout the heart.<sup>33, 34</sup> Sotalol is well absorbed and transferred to reach a fetal steady state level similar to maternal plasma level (F/M ratio 0.7-2.1).<sup>2, 22</sup> The agent is usually well-tolerated and maternal SAEs have not been reported. Maternal sotalol up to 480 mg/day did not cause significant prolongation of neonatal QTc.<sup>35</sup> Symptoms related to β-blockade may include fetal or maternal bradycardia.<sup>1</sup> There is a single case of unexplained fetal death in the absence of fetal hydrops in the literature.<sup>21</sup>

In *summary*, antiarrhythmics act on one or several ion channels and/or the autonomous system. Drug-specific differences in actions and pharmacokinetics likely predetermine the potential of a compound in terminating and, once achieved, in suppressing SVA recurrence.<sup>36</sup> AVRT involves myocardium, the AV node and accessory pathway(s) in the reentrant circuit. Alteration of the conduction and refractoriness properties of any of these tissues may terminate AVRT. **Digoxin** prolongs AV nodal refractoriness. If the prolongation is sufficient, reentry will terminate because the AV node becomes refractory to premature depolarization. **Flecainide** delays the



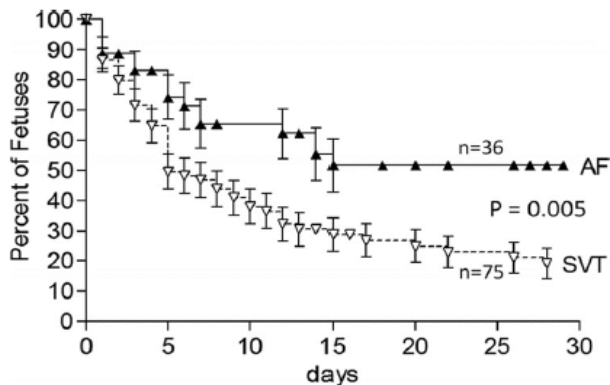
myocardial conduction and disproportionally prolongs refractoriness of the myocardium and the conduction system at faster rates. **Sotalol** delays AV nodal conduction and prolongs the refractory period to electrical stimulation of the myocardial and conduction tissues. Suppression of arrhythmias confined to atrial tissue (AET; AF) is possible by flecainide and sotalol that directly act on atrial cells. Digoxin has probably no such direct effects on atrial cells but slows tachycardia rates, owing to improved ventricular filling with lower atrial pressure and distension. The hemodynamic changes may alter electrical tissue properties and indirectly suppress AF.<sup>37</sup>

## 2.5 EFFICACY OF TRANSPLACENTAL THERAPY.

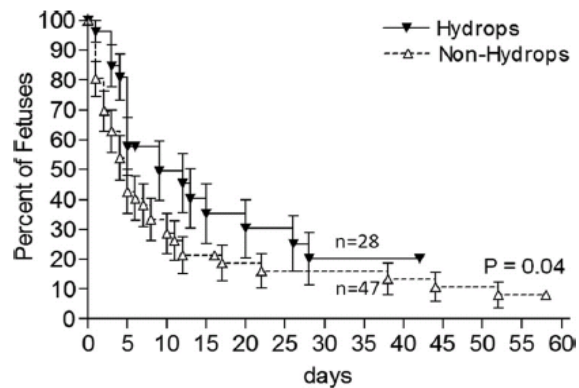
**PROSPECTIVE STUDY.** There are no other prospective randomized studies of fetal SVA therapy to date.

**RETROSPECTIVE STUDIES.** Retrospective studies report inconsistent success rates for all 1<sup>st</sup> line agents in treating fetal SVA.<sup>2</sup> In studies (total n=226) using oral **digoxin** monotherapy, in-utero cardioversion has been reported in 50% to 100% of SVA *without* hydrops, but in <20% of SVA *with* hydrops.<sup>5, 8, 9, 18, 24, 30</sup> **Flecainide** (n=70) has resulted in sinus rhythm in 58% to 100% of SVA cases *without* hydrops and in 43% to 58% of those *with* hydrops.<sup>6, 18, 24, 26, 29, 31</sup> **Sotalol** (n=56) has been successful in 40% to 100% of SVA *without* hydrops, and in 50% *with* hydrops.<sup>21, 22, 29</sup> While the studies confirm that there is no single medication that can convert all fetal SVAs to a normal rhythm, direct comparisons of study results is impossible as study cohorts varied in disease severities, definitions of treatment success, drug doses, schedules, and many other factors. Data on the impact of the same agents as 2<sup>nd</sup> line monotherapy or in combination to treat therapy-resistant SVA is largely unavailable.<sup>2</sup>

**DRUG COMPARISONS.** The only study to directly compare transplacental drug therapies by Jaeggi et al., an initiator of the FAST Therapy Trial, represented the experience of 3 sites, each using a different 1<sup>st</sup> line agent.<sup>1</sup> An adverse primary outcome, defined as a) preterm delivery, b) perinatal death, or c) persistent SVA to birth, was documented in 45% of 75 treated SVT cases (outcome a) 32%; b) 8%; c) 5%) and 58% of 36 treated AF cases (a) 50%; b) 3%; c) 6%), and was mainly related to *incomplete SVA control at the time of the event*. However, Jaeggi's study also demonstrated that the fetal response to treatment independently depended on the *SVA pattern, fetal state* and the *choice of 1<sup>st</sup> line therapy*. AF [Fig. 1] and fetal hydrops [Fig. 2] were independently associated with

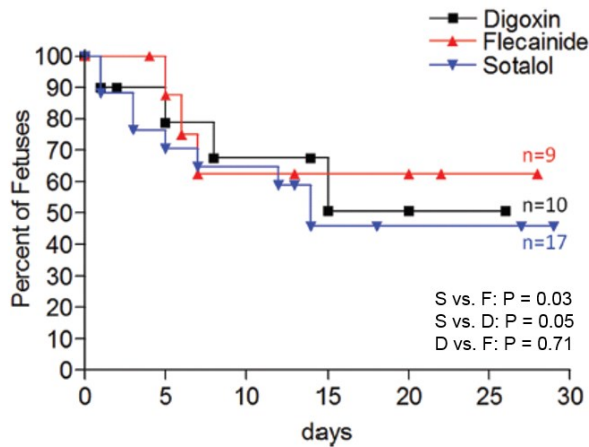


**Fig. 1. Freedom from termination of fetal SVT vs. AF despite drug treatment (n=111).** AF responded more slowly to drug therapy than SVT (HR=2; p=0.005). Cardioversion at 5 and 10 days was achieved in 50% and 63% of fetuses with SVT and in 25% and 41% of cases with AF.

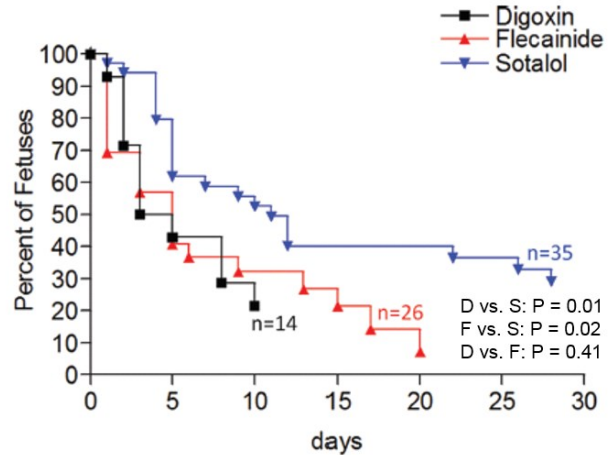


**Fig. 2. Freedom from termination of fetal SVT with and without hydrops (n=75).** Treatment failure was also more likely if SVT was associated with fetal hydrops (HR=1.8; p=0.04) at the time of diagnosis. It took more than twice as long (9 vs. 4 days) for conversion of 50% of SVT cases to a normal rhythm if fetuses were hydropic. 21% of the hydropic cases died.

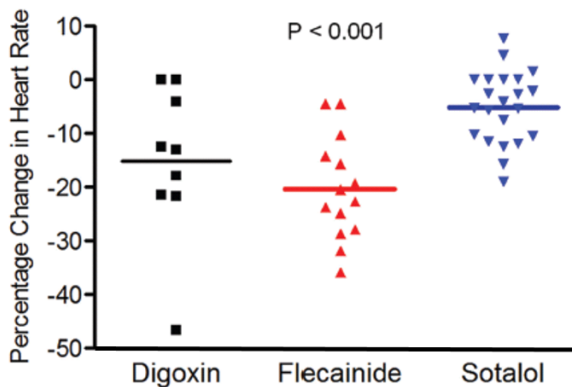
lower cardioversion rates. On the other hand, 1<sup>st</sup> line monotherapy with sotalol resulted in faster/higher AF termination rates [Fig. 3] while flecainide or digoxin was superior in terminating SVT [Fig. 4] and in lowering tachycardia rates if SVA persisted [Fig. 5]. None of the agents as 2<sup>nd</sup> line therapy was associated with a greater rate of SVA termination although **sotalol** tended to be superior for AF. Once fetal SVA was converted to sinus rhythm, chronic drug therapy to birth with the drug(s) that successfully terminated the SVA was used to prevent recurrences. Recurrence of SVT and AF was documented in 8% and 15% of cases during the first month of maintenance treatment.<sup>1</sup>



**Fig. 3. Freedom from termination of fetal AF (n=36):** For patients with AF, in multivariate models adjusted for arrhythmia pattern, 1<sup>st</sup> line sotalol was associated with a greater likelihood of AF termination compared with digoxin (HR: 5.4; p=0.05) or flecainide (HR: 7.4; p=0.03). Time to conversion of 50% was 12 days with sotalol, but not achieved with the other drugs before delivery.



**Fig. 4. Freedom from termination of fetal SVT (n=75):** For patients with SVT, in multivariate models adjusted for hydrops and SVT pattern, the use of flecainide (HR: 2.9; p=0.01) or digoxin (HR: 2.1; p=0.02) as 1<sup>st</sup> therapy were associated with increased likelihood of SVT termination compared to sotalol. The median time to conversion of 50% of cases was 3 days with digoxin, 4 days with flecainide but 12 days with sotalol.



**Fig. 5. Effects of 1<sup>st</sup> line treatment on tachycardia rates.** When incessant SVT (n=23) or AF (n=22) persisted to day 5 of treatment, ventricular rates were lowered more with flecainide and digoxin than with sotalol (p<0.001). This suggests that flecainide and digoxin are similarly effective in reducing the tachycardia to better tolerated rates while sotalol has no or only modest heart rate slowing effects.

*In summary*, our previous study results support the concept that successful transplacental drug therapy and the outcome of the pregnancy significantly depend on any of these three variables:

- The underlying **SVA mechanism** (AF vs. SVT)
- The **fetal state** (fetal hydrops vs. non-hydrops), and
- The primary choice of **antiarrhythmic therapy**

The optimal choice of therapy at the time of a new SVA diagnosis is of critical importance as it is the *only variable* that may be directly influenced by the treating physician's decisions.

While the study by Jaeggi provided new data on the potentials and limitations of prenatal drug therapy and in selecting agents for the FAST Therapy Trial, several limitations inherent to the retrospective study design may limit the validity of some study findings. This includes: a) relatively small case numbers due to the relative rarity of SVA (111 treated cases; 3 therapy arms); b) differences in disease severity among patient cohorts; and c) insufficient data to address AEs and 2<sup>nd</sup> line therapy. One important study conclusion nonetheless was that 1<sup>st</sup> line therapy initiation with only one antiarrhythmic is probably safe *unless fetal heart failure is present* (21% perinatal mortality), leading to this proposal to start with *single drug therapy in the absence of hydrops (RCT Sub-study A and B)* and *dual therapy with hydrops (RCT Sub-study C)*. This approach is also supported by latest clinical data that showed no mortality with the primary use of digoxin and flecainide in fetal SVT *with hydrops*.<sup>38</sup>

**2.6 SAFETY OF TRANSPLACENTAL THERAPY** There is extensive retrospective data on the safe use of digoxin, sotalol, and flecainide, either alone or when used in combinations for this indication, with the limitation that AEs were most likely inconsistently documented and thus underreported in retrospective studies. Although minor drug-related AEs are not infrequent patient complaints based on our own retrospective experience<sup>1</sup> and drug monographs, life-threatening AEs owing to the use of fetal antiarrhythmic drug therapy in predominantly healthy mothers have not been reported.<sup>2, 36</sup> However, virtually all antiarrhythmic agents may have the potential to provoke new or to exacerbate existing arrhythmias. This risk increases with toxic drug levels, maternal heart disease, ventricular arrhythmia, and hypokalemia.<sup>39-41</sup> Previously reported mortality rates of treated fetuses with SVA *without* hydrops were between 0% and 5%, whereas about 20% of fetuses with SVA *with* hydrops had died, usually due to treatment-resistant SVA.<sup>2, 5</sup> In our large experience, we never observed unexpected SAEs, irrespective whether single or multiple drug therapy was used.<sup>1</sup>

*To minimize risks of SAEs* a) only mothers without serious health and pregnancy concerns other than fetal SVA are eligible for participation in the RCTs (**see Section 7.2**); b) the primary physician and participant both are informed about the assigned drug therapy from the time of randomization to study end (open label trial); c) drug dosages will be used that are considered to be safe and effective (**see 7.6**), thus avoiding toxic levels (digoxin) and excessive QTc prolongation >0.5 (sotalol); and d) initiation of therapy is recommended in-hospital to monitor maternal/fetal heart rates and wellbeing, followed by serial outpatient encounter once arrhythmia control is achieved (**see 7.7**).

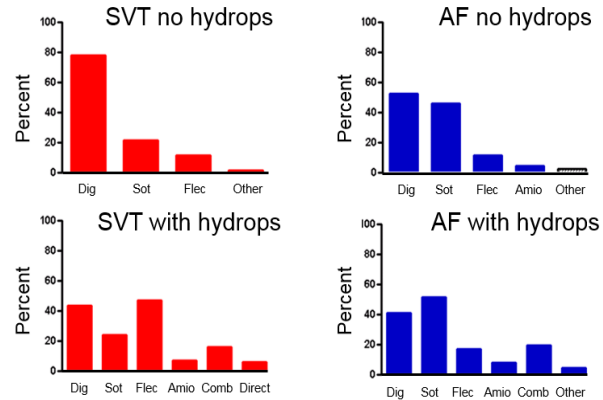
### 3. STUDY FEASIBILITY

**3.1 SURVEYS.** To determine feasibility of the FAST Therapy Trial, we conducted two large surveys.

In **Survey I**, of which 87 tertiary maternal-fetal (47%) and fetal cardiology (61%) sites replied, we determined: a) caregivers responsible for the management of fetal SVA at each site; b) average numbers of treated cases/year and site; c) the willingness to participate in a prospective RCT (94% support) and/or a prospective registry (90% support); d) current 1<sup>st</sup> line drug choices [**Fig. 6**] and e) drug preferences for hypothetical RCTs [**Fig. 7**].

**Fig. 6. Current 1<sup>st</sup> line drug choices (Survey I; n=87)**

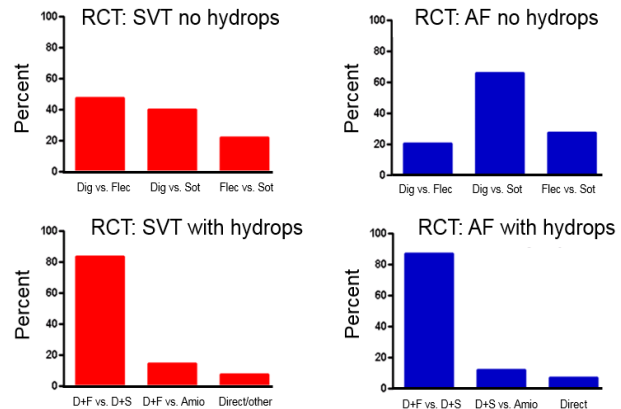
Digoxin was most commonly quoted as 1<sup>st</sup> choice agent to treat SVT and AF without hydrops. If there was fetal hydrops, flecainide for SVT and sotalol for AF were slightly preferred over digoxin. Less than 20% currently use 1<sup>st</sup> line therapy with more than one agent to treat SVA/hydrops despite the slow cardioversion rates to drug monotherapy (Fig. 2) and the high risk of adverse outcome.



**Fig. 7. Elected 1<sup>st</sup> line drug comparisons in potential 2-arms RCTs (Survey I; n=81)**

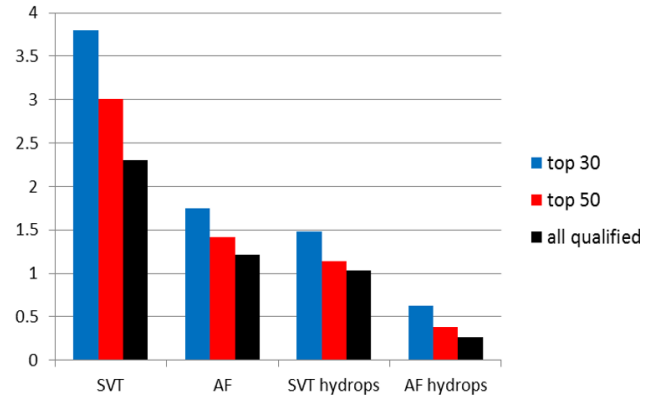
- *SVT without hydrops: digoxin vs. flecainide*
- *AF without hydrops: digoxin vs. sotalol*
- *SVT or AF with hydrops: digoxin plus flecainide vs. digoxin plus sotalol.*

Potential 2-arm comparisons selected in the survey are in agreement with the study results of Jaeggi et al<sup>1</sup>, eliminating the agent that was associated with the weakest cardioversion rate for SVT (sotalol) and AF (flecainide) in the comparisons (Fig. 3-4)



In **Survey II**, we obtained (89 potential study sites, 23 countries): a) numbers of treated SVA cases based on institutional reviews of 2011-2012 [**Fig. 8**], b) expected maternal consent/recruitment rates at each center (mean: 81%), and assessed c) participation rates in the AF/no hydrops RCT (n=75; 86%), SVT/no hydrops RCT (n=76; 87%), SVT/hydrops RCT (n=78; 90%), and/or the registry (n=69; 79%). Of 87 centers willing to participate in at least one RCT, three RCTs were elected by 66 (76%), 2 RCTs by 12 (14%), and 1 RCT by 7 (8%) centers. We also obtained >80 letters of collaboration from major fetal-maternal centers that wish to participate in the FAST Therapy Trial, incl. 10 Canadian sites. All study goals are achievable within <5 years with <50 average sized centers.

**Fig. 8. Average number of treated cases per year of centers that plan to participate in at least one RCT (Survey II; n=87/89 centers).** Data represent the 30 largest centers (blue), the 50 largest centers (red) and all participating centers (black) in the SVT RCT (76/87), AF RCT (75/87) and SVT/hydrops RCT (78/87). SVT, AF and SVT/hydrops account for 50%, 25% and 20% of SVA cases. Sample size calculations (2.11) are based on data of “qualified centers.” No AF/hydrops RCT is planned (5% of SVA cases).



**3.2 SAMPLE SIZE CALCULATIONS.** Based on our survey results and the retrospective study by Jaeggi et al, we expect 70% of SVA cases to be SVT (50% no hydrops; 20% hydrops) and 30% AF (25% no hydrops; 5% hydrops).<sup>1</sup> Survey II suggests that an average of 2.3 SVT/no hydrops, 1.21 AF/no hydrops and 1.03 treated SVT/hydrops cases/year/center will be eligible for RCT enrolment, with average consent rates of 81%. Sample size calculation for 2-arm treatment comparisons was performed using PASS (Power and Sample Size) v12 (NCSS, LLC, Kaysville, Utah, USA). To calculate sample size requirements for this study we expected the proportion of patients with normal primary outcome to be 55% with SVT without hydrops, 30% with AF without hydrops, and 30% of SVT with hydrops with the inferior treatment arm (i.e. the null hypothesis). We aim to detect an improvement of +20% in the proportion of patients with a normal primary outcome with the superior RCT arm (i.e. 75% for SVT without hydrops; 50% for AF without hydrops and SVT with hydrops; i.e. the alternative hypothesis). The test statistic used is the two-sided Likelihood Ratio test which is equivalent to the Wald chi-square for logistic regression models which will be used to analyze our primary outcome. The significance level of the test of significance was targeted at 0.05, with a power of 80%. Assuming those metrics, we will need 550 RCT participants, with a minimum number of patients in each of the three RCTs of:

**AF without hydrops (RCT A):** 186 (93/arm) treated cases ← 232 approached cases with 80% consent rate

**SVT without hydrops (RCT B):** 178 (89/arm) treated cases ← 222 approached cases with 80% consent rate

**SVT with hydrops (RCT C):** 186 (93/arm) treated cases ← 232 approached cases with 80% consent rate

With 50 average sized sites, we anticipate 225 treated patients/year (mean: 4.5) to be approached during the study period which should be sufficient to recruit the required number of patients with *SVT without hydrops (RCT B)* in 1.9 years, *AF without hydrops (RCT A)* in 3.8 years and *SVT without hydrops (RCT C)* in 4.4 years. In contrast, we do not expect sufficient cases for a separate *AF with hydrops* RCT (0.27 cases/year and site). *Study completion <5 years would require a minimum of 20 average sized centers in RCT B (4.7 years), 40 centers in RCT A (4.7 years), and 45 centers in RCT C (4.9 years).* The site investigator will be responsible for recruiting participants and conducting the study at the participating center. There is no data on consent rates for a prospective fetal SVA trial. Survey II suggests average consent rates of 81%. Consent rates are available from other fetal-maternal RCTs. Despite the more invasive nature of these studies, consent was obtained in 71.4% of eligible mothers to study the impact of serial amnioreduction vs. selective fetoscopic laser photocoagulation to treat fetal twin-twin

transfusion syndrome in a US-based study;<sup>42</sup> in 86% of mothers to compare prenatal with postnatal repair of fetal myelomeningocele;<sup>43</sup> and in 86% of mothers to study the impact of fetal endoscopic tracheal occlusion with standard postnatal care for congenital diaphragmatic hernia.<sup>44</sup> As we will not compare experimental but standard therapy, we would expect equal or higher maternal consent rates.

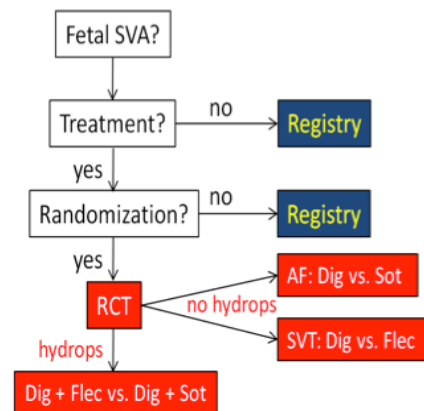
IN *SUMMARY*, most sites contacted in our Surveys agreed that there is a need for prospective studies, and would be willing to participate in sufficient numbers to complete all components of the FAST Therapy Trial with <5 years. Other research collaborations already exist with and among many potential study sites (e.g. TTTS laser interventions; PIAF study; Fetal Intervention Registries; retrospective multi-institutional collaborations (SVA, CHB, Ebstein, etc.). Potential 2-arm comparisons [Fig. 7] are in agreement with our previous study findings<sup>1</sup> that suggested better results with 1<sup>st</sup> line *flecainide or digoxin for SVT* [Fig. 4] and with *sotalol for AF* [Fig. 3]. Health Canada has issued *letters of no objection* for the RCTs.

## 4. STUDY DESIGN

**4.1 TRIAL COMPONENTS.** The FAST Therapy Trial is a prospective trial of patients with a new diagnosis of fetal SVA. The study aims to compare the impact of different perinatal treatment strategies from the time of SVA diagnosis to 30 days after birth or death. Research components as shown in **Figure 9** include:

- **Three prospective RCT sub-studies** to determine the efficacy and safety of specific transplacental drug regimens in suppressing: A) fetal AF *without* hydrops (RCT A); B) SVT *without* hydrops (RCT B); and C) SVT *with* hydrops (RCT C).

*A prospective observational cohort study (FAST Registry)* to document the outcome of patients because randomization is not offered or not possible, non-study 1<sup>st</sup> line medication is used, or observation without treatment is elected (REB Number# 1000048953).



† RCT Sub-studies A, B and C are open label 1 as monotherapy (no hydrops) or as dual therapy maternal and fetal inclusion criteria and none of the between “AF vs. SVT” and “hydrops vs. non-study (Fig. 9). The site investigator will be on in the appropriate RCT arm. Each participant to be used for communication with the site 1 as possible, but not prior to randomization or diagnostic accuracy by reviewing de-identified

baseline fetal SVA tracings and abdomen/chest images, as well as ECG and clinical data of each participant. Once started on 1<sup>st</sup> line therapy, the treating physician will at any time be free to modify and/or change treatment for the remainder of gestation. Patient care maps for the different treatment arms are provided that may help and be used to guide most perinatal management decisions to birth. Maternal questionnaire and, if applicable, case report forms (CRFs) will be used to assess for maternal and fetal AEs and specified outcomes (5.2.1) at each participant encounter.

With 50 centers and 80% consent rates per RCT, actual study periods are expected to take 1.9 years (RCT B: *SVT without hydrops*), 3.8 years (RCT A: *AF without hydrops*), and 4.4 years (RCT C: *SVT with hydrops*), respectively. This will allow postnatal follow-up to a minimum of 30 days after birth of all study participants. Recruitment for the RCT sub-studies will be competitive and once a predetermined number of participants are enrolled, new patients will be considered for the registry only.

**4.3 REGISTRY.** Registry data will be used to determine the outcome of the non-randomized (treated), and untreated SVA study population to examine the impact and outcome of alternative treatment approaches. This includes fetal *AF with hydrops*, which is not studied by a separate RCT due to the rarity of the association.

**4.4 STUDY WITHDRAWAL.** A subject is free to withdraw from participation in the trial at any time, for any reason, specified or unspecified, and without prejudice. The reason for the subject's withdrawal from the study (if given) will be documented in the *Study Completion/Exit Form*. If the subject withdraws, data that has already been collected up to that point in time will be kept (as indicated in the patient informed consent).

**4.5 PARTICIPANT REPLACEMENT.** Study participants withdrawing from the trial will be replaced 1:1 to obtain the target number of evaluable participants per RCT arm.

**4.6 NONPARTICIPATION.** If an eligible patient has been approached for the RCT but elects to not participate the screening information should still be documented in REDCap, including the patient's decision to not participate. Collection of basic screening information by the sponsor is important as it will allow an analysis of patient willingness to participate, of excluded cases and an estimation of the number of total SVA cases. Moreover, information on the rate of non-participation will be essential for future publications.

## 5. STUDY SAFETY

**5.1 SAFETY PROCEDURES.** The FAST RCTs will assess *standard prenatal treatment* that has been used for decades because the fetus suffers from a life-threatening yet treatable cardiac condition and other management options including direct treatment or premature delivery are considered more invasive, more harmful, or both. Perinatal demise is not an unusual outcome of hydropic fetuses with SVA, irrespective of the choice of treatment. Health Canada, FDA (US) and MHRA (UK) have approved all three RCT sub-studies. There is extensive data on the safe use of the study agents for this indication. Minor drug-related maternal AEs are not infrequent [monographs],<sup>1</sup> but maternal SAEs owing to fetal antiarrhythmic drug therapy have not been reported.<sup>2,36</sup> However, virtually all antiarrhythmics have proarrhythmic potentials to provoke new or exacerbate existing



arrhythmias. This risk increases with toxic drug levels, maternal heart disease, preexisting ventricular arrhythmia, and hypokalemia.

Procedures for study participants to minimize the risk of SAEs include:

- only mothers without serious health and pregnancy concerns other than fetal SVA are eligible for participation in RCT sub-studies (**see 7**);
- the primary physician and participant both are informed about the assigned drug therapy from the time of randomization to study end (open label trial);
- drug dosages will be used that are considered to be safe and effective, thus avoiding toxic levels (digoxin) and excessive QTc prolongation >0.5 (sotalol); d) concomitant medication (7.6.2) that may interact with a study drug are not to be used or, if no alternative exists, used with caution during the trial; and
- initiation of therapy is recommended in-hospital to monitor maternal/fetal heart rates and wellbeing, followed by serial outpatient encounter once arrhythmia control is achieved.

**5.2 ADVERSE EVENT ASSESSMENT AND DOCUMENTATION.** A main objective of FAST RCTs is patient safety. This is accomplished by the systematic recording of AEs.

**Adverse Event (AE):** is defined as **any untoward medical occurrence of a symptom that may or may not have a causal relationship with the treatment used.** Examples include a rash noted during a physical exam, abnormal lab results, or a change from a baseline condition.

Failure of the drug does not constitute an AE. Sources of information will include observation (physical exam; ECG; echo; lab result), patient statement, patient charts, and serial assessment at each encounter by questionnaire for changes from baseline (↑ severity/frequency of pre-existing symptom(s)) or new AEs).

It will be the responsibility of the primary physician to identify, and to classify the seriousness, severity, causality and expectedness of an AE as follows:

***a) Assessment if event qualifies as serious:***

**Serious Adverse Event (SAE):** A SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity
- Results in congenital abnormalities or birth defect

Other events may be treated as SAEs if the Principal Investigator considers it to be an important medical event that may jeopardize the participant or require intervention to prevent one of the other outcomes listed above.



**b) Severity assessment:**

<b>Mild</b>	Events are considered MILD if signs/symptoms are mild, clinical relevance is marginal, laboratory findings are asymptomatic and no specific medical intervention is required.
<b>Moderate</b>	Events are considered MODERATE if they require minimal, local, or non-invasive intervention only.
<b>Severe</b>	Events are considered SEVERE if they interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

**c) Causality assessment:**

<b>Definitely related</b>	There is a certainty that the event is related to the study drug(s).
<b>Probably related</b>	There is high likelihood that the event is related to the study drug(s).
<b>Possibly related</b>	There is a likelihood that the study drug(s) is the cause of the event, but other causes cannot be ruled out.
<b>Unlikely related</b>	It is not likely that the event is related to the study drug(s), and other more likely causes are present.
<b>Unrelated</b>	Evidence exists that the event is related to something other than a study drug.

**d) Expectedness assessment:**

An event is considered unexpected if the nature, severity or frequency **is not consistent with the risk information listed in the *Product Monograph***.

Pregnancy- and treatment-related AEs will be documented by the site investigator. Prior to the start of drug therapy (pretreatment forms), a thorough medical history should be obtained to document all preexisting maternal symptoms, complaints and health concerns. As many pregnancy related symptoms are intermittent in nature, a thorough history including variations in severity and frequency should be taken. AEs should be reassessed at each participant encounter. If signs or symptoms remain similar to baseline or are less in severity, frequency, or both, they will be considered within the usual range and do not need to be documented as AEs. In contrast, signs and symptoms that are new or, if preexisting, are more frequent/severe, need to be documented, assessed for severity and causality, and followed up until resolution.

### 5.2.1 ASSESSMENTS OF COMMON PREGNANCY, BIRTH AND NEONATAL EVENTS

The following common pregnancy, delivery, and neonatal events should be recorded in source documents (clinic notes or CRFs) if they occur and *are only requested be recorded on AE worksheets if the PI or MD delegate feel that the event may be drug related* and/or determine that a full assessment is required.

#### Prenatal Maternal Events:

- Accidents or injuries
- Anaemia
- Back pain
- Bacterial or viral infections
- Contractions
- Diabetes and associated complications
- Gestational hypertension/ worsening of hypertension
- Heartburn
- Hemorrhoids; varicosis
- Hospitalization for obstetrical reasons
- Hypoglycemia requiring treatment
- Leg muscle cramps
- Ligament pail
- Pre-eclampsia and eclampsia
- Vaginal bleeding or discharge

- Birth injury
- Neonatal aspiration, hypoxia
- Respiratory distress of newborn
- Hyperbilirubinemia
- Neonatal hypoglycemia
- Neonatal Infection
- Hospitalization for observation after birth
- Hypoglycemia requiring treatment
- Genetic disorder

#### Intrapartum and Postpartum Maternal Events

- Hospitalization for delivery
- Anesthesia-related complications
- Cesarean delivery
- Hysterectomy
- Postpartum depression
- Postpartum hemorrhage
- Infections
- Ventilation
- Birth related complications

#### Infant Events:

**5.3 ADVERSE EVENT REPORTING.** Completed AE worksheets of all documented events will be captured on REDCap. All SAEs irrespective of their relatedness to the therapy or study procedures must be reported to the Sponsor. The site investigator must pursue any AE and if possible obtain information adequate both to determine the outcome and assess the relatedness to treatment so it can be determined by the PI and Sponsor whether it meets the criteria of a SUADR.

**Serious Unexpected Adverse Drug Reaction (SUADR):** All noxious and unintended responses to an investigational product related to any dose which is serious and unexpected.

## REPORTING PROCEDURES

Any SAE (irrespective of relatedness to study procedures) must be notified to the study Sponsor (SickKids) immediately upon the investigator becoming aware of the event (see guidelines below).

Completed SAE reporting forms are to be sent to:

- **Sponsor (SickKids) via fax +1-416-813-2148 or E-mailed to [Fast.trial@sickkids.ca](mailto:Fast.trial@sickkids.ca)**

SERIOUS ADVERSE EVENTS (Recorded by site investigator)	REPORTING BY SITES TO SPONSOR	REPORTING BY SITES TO LOCAL REB
<i>Unexpected</i> , possibly, probably or definitely related to medication or study procedures	<ul style="list-style-type: none"> <li>• Notification within 24 hours</li> <li>• Full report to follow as requested by the Sponsor</li> </ul>	<ul style="list-style-type: none"> <li>• According to Institutional guidelines</li> </ul>
<i>Expected</i> , possibly, probably or definitely related to medication or study procedures	<ul style="list-style-type: none"> <li>• Notification within 24 hours</li> <li>• Full report to follow as requested by the Sponsor</li> </ul>	<ul style="list-style-type: none"> <li>• According to Institutional guidelines</li> </ul>
SAEs assessed to be <i>unrelated</i> to medication or study procedures	<ul style="list-style-type: none"> <li>• Notification within 24 hours</li> <li>• Follow-up report only if requested by the Sponsor</li> </ul>	<ul style="list-style-type: none"> <li>• According to Institutional guidelines</li> </ul>

The Sponsor will work with the National Coordinating centers in each regulatory jurisdiction to report events as required to the appropriate regulatory authority.

**5.4 EARLY STOPPING RULE.** All three RCT sub-studies, individually or as a group, can be temporarily stopped for safety reasons at any time, at the discretion of the Data & Safety Monitoring Board [*DSMB Charter*; also see 6.4]. An RCT can be stopped for benefit at the time of an interim analysis if results unequivocally favor one treatment arm over the other at the  $p < 0.001$  level. If one is demonstrably superior to the other, it would be unethical to continue the sub-study as is. Stopping of the study for benefit will be decided based on discussions of the DSMB with the study PI and the Trial Steering Committee.

## 6. STUDY MANAGEMENT & RESPONSIBILITIES

**6.1 MEDICAL OVERSIGHT** (Medical oversight) of participants at each study site will be the responsibility of the PI at each centre. Procedures for medical oversight must be implemented at each site and responsibilities in care and assessments delegated to appropriately trained staff. Documentation of this oversight must be maintained for the length of the trial (as required by your institution and regulatory authority).

**6.2 TRIAL OVERSIGHT** will be maintained by the Sponsor-Investigator, *Edgar Jaeggi*.<sup>1, 2, 7, 9, 23, 36, 45-52</sup>. He and his team of physicians and trial support staff will oversee the conduct of the study.

**6.3 DATA MANAGEMENT.** The password-protected REDCap data management system ([www.project-redcap.org](http://www.project-redcap.org)) will be used to enter de-identified patient data by the participating sites. Credentialing to access REDCap will be managed centrally by the FAST Trial study team in cooperation with the Cardiovascular Data Management Centre (CVDMC). Individual access will be limited to data from individual sites. The system is deployed through a secured/encrypted server hosted at SickKids and will be managed by an experienced Clinical Research Project Manager (statistician and database manager) from the CVDMC. REDCap is available anytime, anywhere in the world, is completely automated and will allow new patient input and randomization instantaneously once a center becomes eligible to participate in the FAST Therapy Trial; thereafter all required CRFs (incl. patient characteristics, treatment information, outcomes) will be available with basic data validation at the time of data entry (physiological range, validation of time interval, pre-determined coding, required fields, etc.). Regular updates of key findings will be requested from the site investigator up to 1 month of life. Once completed, participant data will be verified for completeness and validity by the FAST Trial team, and any queries will be sent to the site investigator. Once the record is deemed complete/valid, it will be locked so that further edits will not be possible to ensure highest data quality.

**6.4 DATA & SAFETY MONITORING BOARD (DSMB).** An independent DSMB of 4 members will monitor the progress of the RCT sub-studies and review the safety data [DSMB Charter of the Randomized Clinical Sub-trials]. The DSMB will review the result of interim analyses and other safety data and, if required, will provide recommendations to the study sponsor including to stop the trial if there are safety concerns.

**6.5 STEERING COMMITTEE MEMBERS.** The clinical research aspect of this study has been developed and will be conducted under the supervision of a highly experienced multidisciplinary team of experts in the field who collectively have published >1,300 refereed papers, incl. 45 on fetal tachyarrhythmia and >50 RCTs. The committee includes the PI, *Edgar Jaeggi*, and 10 co-investigators who initiated/designed the FAST Therapy Trial, including this Protocol and the Care Maps. Members include: *Brian McCrindle*, Director of the Cardiovascular Clinical Research Unit at SickKids Heart Center; *Martin Offringa*, Head of the Child Health Evaluative Science Program at SickKids with a vast experience in the design, conductance and reporting of evidence-based clinical trials in children; *Nico Blom*, *Phil J Saul*, *Julene Carvalho*, *Bettina Cuneo*, *Anita Moon-Grady*, *Ulrich Gembruch* and *Greg Ryan*, who are leading experts in electrophysiology, cardiology and maternal-fetal medicine, respectively, and last but not least, *Ed Kelly* who directs a large Neonatal Follow-up Clinic. Members of the Steering Committee may be consulted if there is disagreement between a study site and the Echo Core Lab regarding a fetal diagnosis. The committee will assist in interpretation of study outcome data and with the development of practice guidelines and interdisciplinary knowledge transfer. The committee will communicate via e-mail and have intermittent conference calls to discuss study issues. Annual meetings are planned to discuss study progress and any relevant issues. These meetings may also include national and site investigators.

**6.6 NATIONAL COORDINATORS.** In countries with larger numbers of participating centers investigators have been identified to function as National Coordinators. Their role will be to assist the FAST Trial Team by providing regional oversight and support for running of the RCTs. Responsibilities of National Coordinating Centers may include help with obtaining ethical approval, applications/reporting to the local regulatory authorities

and providing logistic support to sites if required. The study sponsor will assist all sites including centers of countries without a national coordinator.

## 7. CONDUCT OF THE RCTs

The Table of Events below summarizes the different study steps from the time of prenatal identification and randomization to study end as they relate to the RCT sub-studies.

Procedures and Tests	Pre-treatment	Fetal Treatment		Postnatal Birth to 30(+) days
		Day 1	Day 2 - Birth	
Fetal echo: Diagnosis -SVA (M-mode; Doppler) - Fetal state	X diagnosis and data ⬆ Images within 1 week recommended		X data each visit ⬆ if changed	
Maternal 12-lead ECG	X required prior to treatment start ⬆		X recommended within 1 week of treatment start and repeated at every significant change in treatment/increase in dose ⬆ if changed	
Maternal exams: - BP, HR	X		X recommended within 1 week of treatment start and during maintenance therapy	
Maternal tests: - K, Ca - serum creatinine	X			
Maternal and pregnancy history	X			
Maternal consent	X			
Eligibility Assessment - PI	X			
Randomization	By sites in REDCap			
Hospitalization		Recommended	If indicated	If indicated
Treatment initiation		X		
<b>Review of current treatment</b> - Drugs, dosages, intervals			X each visit	X
<b>Review of clinical findings</b>			X each visit	X
<b>Review of test results</b> - Digoxin level (if relevant)			X each visit	
- Home fetal heart rate monitor (FHRM)			⬆ or enter data	
<b>Adverse event assessment</b>			X each visit	X
<b>Compliance assessment (1st line therapy)</b>			X each visit	
<b>Review of prenatal outcome</b>			X at birth/IUD	
<b>Neonatal 12-lead ECG in sinus rhythm</b>				X ⬆
<b>Neonatal 12-lead ECG tracing in SVA</b>				X ⬆ if present
<b>Review of neonatal outcome</b>				X at 30(+)days/NND
<b>Review of maternal outcome</b>				X

X = data entry into REDCap, ⬆= uploaded in REDCap

Patient identification, data entry, eligibility screening, randomization (Pre-treatment) and treatment initiation (Day 1) are to occur on the same day if there is an immediate need of fetal treatment.

**7.1 PATIENT IDENTIFICATION.** The site investigator will be responsible for identifying and recruiting RCT participants and conducting the study at the participating center. The investigator will inform a patient who fulfills eligibility criteria about the study early on with the help of a *Patient Brochure*.

Study Logs for screening and enrolment are to be kept securely at sites with access only to FAST study team members. These Logs will be de-identified prior to inspections and audits or if requested by the Sponsor for monitoring purposes. De-identification is also necessary before being sent to the Sponsor at end of study.

A *Screening Log* of all patients screened should be kept with the following information: screening date, patient name, institutional number, confirmation of sub-study screened for, eligibility status, enrolment status and a reason if not enrolled.

Once patients have consented to participate in the study, screened for eligibility and are enrolled into the study, their information should be entered into an *Enrolment Log* with the following information: participant's name, study ID number, institutional number, date and time of enrolment, study enrolled in, as well as an indication if and why a participant has withdrawn. Once a baby is born to a mother in the study, sites will need to keep a *Child Enrolment Log* with the child's name and institutional number, as well as the mother's corresponding study ID number.

**7.2 ELIGIBILITY CRITERIA.** Subjects are eligible for participation in an RCT sub-study if they meet ALL of the following inclusion criteria and NONE of the exclusion criteria. All subjects will be screened by Investigators for study eligibility prior to randomization and enrolment.

**INCLUSION CRITERIA:**

- Mother has provided written informed consent to participate in the RCT
- Fetal AF *without* hydrops (RCT A) or SVT *without* hydrops (RCT B) or SVT *with* hydrops (RCT C)
- Tachyarrhythmia that is significant enough to justify immediate transplacental pharmacological treatment:
  - Tachycardia  $\geq 170$  bpm during  $\pm 100\%$  of time ( $\leq 30$  0/7 weeks of gestation)
  - Tachycardia  $\geq 180$  bpm during at least 10% of observation time
  - Tachycardia  $\geq 280$  bpm
  - Tachycardia with fetal hydrops
- Gestational age  $> 12$  0/7 weeks and  $< 36$  0/7 weeks at time of enrolment
- Untreated tachycardia at time of enrolment
- Singleton Pregnancy
- Healthy mother with  $\pm$  normal pre-treatment cardiovascular findings:
  - ECG within normal range (sinus rhythm; QTc  $\leq 0.47$ s; PR  $\leq 0.2$  s; QRS:  $\leq 0.12$  s; insignificant anomalies; isolated premature beats; isolated complete right bundle branch block; non-specific ST-T segment changes allowed)

- Maternal resting heart rate of 50 bpm or above
- Maternal systolic BP of 85 mm Hg or above

#### EXCLUSION CRITERIA:

- AF *with* hydrops (condition is too infrequent to be studied in a separate RCT sub-study; eligible for Registry)
- Any maternal-fetal conditions associated with high odds of premature delivery or death other than tachycardia (e.g. severe IUGR; premature rupture of membrane; life-threatening maternal disease (incl. pre-eclampsia; HELLP syndrome); severe congenital fetal abnormalities (T 13 or 18; surgery or death expected < 1 month))
- History of significant maternal heart condition (open heart surgery; sick sinus syndrome; channelopathy (long QT, Brugada syndrome); ventricular tachycardia; WPW syndrome; high-degree heart block; cardiomyopathy)
- History of significant maternal obstructive airway disease including asthma
- Current therapy with the following medications:
  - antiarrhythmic drugs
  - Pentamidine
- Maternal serum potassium level <3.3 mmol/L / <3.3 mEq/L
- Maternal ionized serum calcium level of <1 mmol/L / <4 mg/dL) or total serum calcium level <2 mmol/L / <8mg/dL
- Maternal serum creatinine level > 97.2 µmol/L (>1.1 mg/dl)

**7.3 INFORMED CONSENT (IC)** The consent process at each site will be performed as approved by local REB or as per institutional practices. The study is explained to the patient in detail, including the alternatives (registry, non-participation) and any questions are answered prior to signing the consent form. The person obtaining consent must co-sign the form with date and time. A copy of the consent form must be given to the patient.

**7.4 PATIENT DATA ENTRY.** Completion of the enrolment and randomization process requires submission of the following baseline information into the patient's electronic REDCap form *prior* to any treatment:

- Name and center of the site investigator, incl. contact information
- SVA: date/gestational age at diagnosis, mechanism, pattern, rate and AV relationship
- Fetal state: presence/location of effusion(s), skin edema, and fetal movements
- Confirmation of enrolment into prospective randomized trial and selection of the sub-study
- Checklist of eligibility criteria for participation

Following randomization and treatment initiation, sites must upload *de-identified images* to REDCap that document the pretreatment fetal arrhythmia mechanism and health state (M-mode and/or Doppler still images, 2-dimensional images of the fetal abdomen/chest for proof of hydrops) and maternal 12-lead ECG for review by the Sponsor Echo Core Lab. Moving clips confirming the fetal SVA mechanism should also be sent via secure file transfer for review by the FAST Trial Echo Core Lab. If de-identification is not possible at the site, an arrangement can be made with the Sponsor to have images and clips sent via secure file transfer for de-identification prior to storage.

**7.5 DATA REVIEW.** Accurate differentiation between “AF vs. SVT” and “hydrops vs. non-hydrops” is critical for the randomization into the appropriate sub-study. SickKids will function as the Echo Core Lab Facility to review patient diagnosis and fetal state to determine if the initiated drug therapy is appropriate. The Core Lab provides support to ensure accurate diagnosis and classification and if requested will provide a review of findings within 48 hours. Other Core Lab physicians or steering committee members will arbitrate if there is no agreement in diagnosis with the site investigator. This approach will avoid inaccuracies in diagnosis and study results.

**7.6 RANDOMIZATION TO FIRST LINE THERAPY.** An individual ID code is assigned by REDCap at first data entry to protect patient privacy. Once participant screening, eligibility data, and confirmation of consent data has been entered into REDCap, they will be asked to confirm diagnosis and then be allowed to randomize to a drug assignment in the selected treatment arm.

Participants will be randomized into one of two possible 1<sup>st</sup> line therapy arms, which either will be started as monotherapy (AF or SVT without hydrops) or as dual therapy (SVT with hydrops). First line drug therapy is pre-defined including the initial dose and mode of administration:

### **AF WITHOUT HYDROPS (RCT A): DIGOXIN vs. SOTALOL**

#### **RCT A ARM 1: DIGOXIN**

Aim: therapeutic maternal trough level of 1.0-2.0 ng/ml or 1.3-2.6 nmol/L (please verify the units your laboratory reports).

→ *Oral or intravenous* loading dose: **Initiate treatment with 0.5 mg Digoxin q 12 h** (total 4 doses over 48 hours) followed by:

→ *Oral maintenance dose:* it is recommended to obtain maternal digoxin trough level 12 hours after the 4<sup>th</sup> loading dose just prior to the administration of the 1<sup>st</sup> maintenance dose\* → await the result and adjust the 1<sup>st</sup> maintenance dose according to the trough digoxin level as followed:

(\*alternatively, a digoxin level may be obtained prior to the 4<sup>th</sup> dose to adjust the 1<sup>st</sup> maintenance dose if levels are not rapidly measured in your center)

<b>Trough level (nmol/L)</b>	<b>Trough level (ng/ml)</b>	<b>Maintenance digoxin dose</b>	<b>Route</b>
2.6 to <2.9	2 to <2.3	0.25 mg/day	<i>Oral</i>
1.9 to <2.6	1.5 to <2	0.375 mg/day	<i>Oral</i>
1.5 to <1.9	1.2 to <1.5	0.5 mg/day	<i>Oral</i>
1.0 to <1.5	0.8 to <1.2	0.75 mg/day	<i>Oral</i>
<1.0	<0.8	1 mg/day	<i>Oral</i>
≥2.9	≥2.3	0 mg/day until digoxin level is <2 ng/ml	

→ recommended to repeat maternal trough level until steady state therapeutic drug levels are obtained. *If using IV Digoxin loading see additional recommendations for IV Digoxin administration below.*

#### **RCT A ARM 2: SOTALOL**

**Initiate treatment with oral Sotalol 80 mg TID or 120 mg BID (240 mg/day).**



**SVT WITHOUT HYDROPS (RCT B): DIGOXIN vs. FLECAINIDE****RCT B ARM 1: DIGOXIN**

Aim: therapeutic maternal trough level of *1.0-2.0 ng/ml* or 1.3-2.6 nmol/L (please verify the units your laboratory reports).

→ *Oral or intravenous loading dose: Initiate treatment with 0.5 mg Digoxin q 12 h* (total 4 doses over 48 hours) followed by:

→ *Oral maintenance dose:* it is recommended to obtain maternal digoxin trough level 12 hours after the 4<sup>th</sup> loading dose just prior to the administration of the 1<sup>st</sup> maintenance dose\* → await the result and adjust the 1<sup>st</sup> maintenance dose according to the trough digoxin level as followed:  
(\*alternatively, a digoxin level may be obtained prior to the 4<sup>th</sup> dose to adjust the 1<sup>st</sup> maintenance dose if levels are not rapidly measured in your center)

<b>Trough level (nmol/L)</b>	<b>Trough level (ng/ml)</b>	<b>Maintenance digoxin dose</b>	<b>Route</b>
2.6 to <2.9	2 to <2.3	0.25 mg/day	<i>Oral</i>
1.9 to <2.6	1.5 to <2	0.375 mg/day	<i>Oral</i>
1.5 to <1.9	1.2 to <1.5	0.5 mg/day	<i>Oral</i>
1.0 to <1.5	0.8 to <1.2	0.75 mg/day	<i>Oral</i>
<1.0	<0.8	1 mg/day	<i>Oral</i>
≥2.9	≥2.3	0 mg/day until digoxin level is <2 ng/ml	

→ recommended to repeat maternal trough level until steady state therapeutic drug levels are obtained.

*If using IV Digoxin loading see additional recommendations for IV Digoxin administration below.*

**RCT B ARM 2: FLECAINIDE**

Aim (if available): therapeutic maternal drug level of *0.2-1 µg/ml*

**Initiate treatment with oral Flecainide 100 mg TID (300 mg/day).**

**SVT WITH HYDROPS (RCT C): DIGOXIN PLUS FLECAINIDE vs. DIGOXIN PLUS SOTALOL****RCT C: ARM 1 DIGOXIN Plus FLECAINIDE****DIGOXIN**

Aim: therapeutic maternal trough level of *1.5-2.0 ng/ml* or 1.9 – 2.6 nmol/L (please verify units that your laboratory reports).

→ Intravenous or oral loading dose: **Initiate treatment with 0.5 mg Digoxin q 8 h** (total 4 doses over 32 hours)

→ *Maintenance dose*: It is recommended to obtain maternal digoxin trough level preferably 10-12 hours after the 4<sup>th</sup> loading dose, prior to administrating the 1<sup>st</sup> maintenance dose. Adjust the 1<sup>st</sup> maintenance dose according to the trough digoxin level as followed:

<b>Trough level (nmol/L)</b>	<b>Trough level (ng/ml)</b>	<b>Maintenance digoxin dose</b>	<b>Route</b>
2.6 to <2.9	2 to <2.3	0.25 mg/day	<i>Oral</i>
1.9 to <2.6	1.5 to <2	0.375 mg/day	<i>Oral</i>
1.5 to <1.9	1.2 to <1.5	0.5 mg/day	<i>Intravenous or Oral</i>
1.0 to <1.5	0.8 to <1.2	0.75 mg/day	<i>Intravenous or Oral</i>
<1.0	<0.8	1 mg/day	<i>Intravenous or Oral</i>
≥2.9	≥2.3	0 mg/day until digoxin level is <2 ng/ml	

→ recommended to repeat maternal trough level until steady state therapeutic drug levels are obtained in the upper therapeutic range.

*If using IV Digoxin see additional recommendations for IV Digoxin administration below.*

#### **PLUS FLECAINIDE:**

Initiate above Digoxin treatment in combination with **oral Flecainide 100 mg TID** (300 mg/day).

#### **RCT C ARM 2: DIGOXIN PLUS SOTALOL:**

##### **DIGOXIN**

Aim: therapeutic maternal trough level of 1.5-2.0 ng/ml or 1.9 – 2.6 nmol/L (please verify units that your laboratory reports).

→ Intravenous or oral loading dose: **Initiate treatment with 0.5 mg Digoxin q 8 h** (total 4 doses over 32 hours)

→ *Maintenance dose*: It is recommended to obtain maternal digoxin trough level preferably 10-12 hours after the 4<sup>th</sup> loading dose, prior to administrating the 1<sup>st</sup> maintenance dose. Adjust the 1<sup>st</sup> maintenance dose according to the trough digoxin level as followed:

<b>Trough level (nmol/L)</b>	<b>Trough level (ng/ml)</b>	<b>Maintenance digoxin dose</b>	<b>Route</b>
2.6 to <2.9	2 to <2.3	0.25 mg/day	<i>Oral</i>
1.9 to <2.6	1.5 to <2	0.375 mg/day	<i>Oral</i>
1.5 to <1.9	1.2 to <1.5	0.5 mg/day	<i>Intravenous or Oral</i>
1.0 to <1.5	0.8 to <1.2	0.75 mg/day	<i>Intravenous or Oral</i>
<1.0	<0.8	1 mg/day	<i>Intravenous or Oral</i>
≥2.9	≥2.3	0 mg/day until digoxin level is <2 ng/ml	

→ recommended to repeat maternal trough level until steady state therapeutic drug levels are obtained in the upper therapeutic range.

*If using IV Digoxin see additional recommendations for IV Digoxin administration below.*

## PLUS SOTALOL

Initiate above Digoxin treatment in combination with **oral Sotalol 160 mg BID** (320 mg/day).

### IV DIGOXIN: additional recommendations

For RCT A, B or C Digoxin can be administered as oral tablets or IV. For IV the Digoxin Injection can be administered undiluted or diluted with a 4-fold or greater volume of 0.9% NaCl injection, or 5% Dextrose Injection. The use of less than a 4-fold volume of diluent could lead to precipitation of the digoxin. Immediate use of the diluted product is recommended. Slow infusion of digoxin over a period of 5 minutes or longer is preferable to bolus administration. Rapid infusion of digitalis glycosides has been shown to cause systemic and coronary arteriolar constriction, which may be clinically undesirable. Mixing of intravenous digoxin with other drugs in the same container or simultaneous administration in the same intravenous line is not recommended.

### 7.6.1 CONCOMITANT MEDICATIONS

Medication to be avoided during trial participation or, if no alternative exists, used with caution and appropriate monitoring of the QTc, include medications that prolong QT and/or increase risk for Torsades de Pointes (TDP) (List available online at: <https://crediblemeds.org/healthcare-providers/>). Concomitant medication use of pentamidine is to be avoided and additional anti-arrhythmics to be used with caution. See relevant drug monographs for detailed information on precautions and possible drug interactions.

## 7.7 STUDY CONDUCT

**PATIENT CARE.** The treating physician will be responsible for the medical care of enrolled participants and medical oversight will be the responsibility of the local PI. The type and frequency of standard clinical care patient assessments, should not differ from a non-study participant with the same clinical findings. The medical management of study participants should also not differ from a non-study patient with comparable clinical findings. This includes, in agreement with accepted management guidelines<sup>53</sup>, the *recommendation* to commence 1<sup>st</sup> line treatment as well as any significant changes in drug therapy in-hospital to allow close monitoring of the fetal-maternal treatment effects and well-being by ECG, echocardiograms, digoxin level, and biophysical profile, until fetal cardioversion or heart rate control is achieved. After discharge from hospital, serial fetal heart rate monitoring to birth by the physician (usually by weekly fetal echocardiograms) and the mother (by daily Doppler monitoring at home) is *recommended* to detect SVA recurrences and to allow treatment adjustments, as required.

What will differ from standard procedures is the requirement to assess and document AEs, including whether the event is serious, the severity, causality and expectedness of the event, as well as to follow-up on and document the outcome. The sponsor PI (Dr. Edgar Jaeggi and his team) will assume the role of Medical Monitor/Advisor and should be contacted for questions regarding the study and patient safety (e-mail: FAST.Trial@sickkids.ca).

**TREATMENT.** All management decisions after initiation of the first-line treatment will be at the discretion of the primary physician. This means that the responsible physician is at any time free to adjust the dosage of 1<sup>st</sup> line medication, to add or switch to a 2<sup>nd</sup> line agent, or to deliver a fetus based on his/her own clinical judgment. It is

however important to recognize that 1<sup>st</sup> line treatment effects are incremental and it will take several days to reach therapeutic fetal drug levels with transplacental medication. A *premature change to 2<sup>nd</sup> line therapy prior to 3-7 days of therapy is therefore not advised* unless there is significant worsening of the fetal state (e.g. new hydrops), the SVA pattern (>20% increase in SVA rates and duration), or both. Members of the FAST Trial steering committee have developed consensus-based recommendations [Care Maps] to adjust the prenatal pharmacotherapy to the most common treatment outcomes and clinical scenarios, e.g. if 1<sup>st</sup>, 2<sup>nd</sup> or 3<sup>rd</sup> line treatment appears ineffective. Care Map recommendations may include: a) no change in therapy (sinus rhythm; ↓ SVA <10% of time); b) escalation of drug dose (some SVA response); or c) addition of or change to different medication (no SVA response). The responsible physician is free to follow the recommendations or to elect treatment that differs from the Care Map. Cross over to a different medication, fetal demise, preterm delivery, and SVA that persists to birth will be considered as *1<sup>st</sup> line treatment failure*. Removal of an agent from treatment following sustained conversion to a normal rhythm (*treatment success*) does not constitute treatment failure.

Following sustained conversion to a normal rhythm of at least 24 hours (*acute 1<sup>st</sup> line treatment success*), it is recommended to not change the successful treatment until birth if the treatment is tolerated and the SVA does not recur. Any new documentation of fetal SVA on maintenance therapy that is *confirmed by fetal echocardiography or by heart rate monitoring during labor* will be considered as *maintenance treatment failure*. Near-complete suppression of SVA does usually not require a change in maintenance therapy. Maternal drug therapy will be maintained until time of delivery and discontinued immediately thereafter. The *choice of postnatal neonatal drug therapy* will be at the discretion of the primary physician. Postnatal outcomes will be assessed to a minimum of 1 month of age.

**7.8 PROCEDURES OUTSIDE OF STANDARD CARE.** The conduct of the RCT sub-studies requires procedures that are not part of usual patient management and documentation of findings. This includes:

- The process of randomization to 1<sup>st</sup> line therapy
- The mode of supply and dispensation of 1<sup>st</sup> line medication
- Home fetal heart rate monitoring (FHRM) offered to participants
- The documentation of de-identified study results in CRFs and REDCap
- Participant questionnaires (AEs and fetal heart rate monitor), medication diary, fetal heart rate monitoring log
- AE assessment and reporting
- Adherence rate to treatment assessment

**DATA DOCUMENTATION:** The table of events summarizes the study conduct and procedures

**PRENATAL.** Following randomization and treatment initiation, sites must upload *de-identified images* to REDCap of pre-treatment M-mode and/or Doppler still images, 2-dimensional images of the fetal abdomen, and 12-lead maternal ECG for review and confirmation of diagnosis by the FAST Trial Echo Core Lab. Moving clips confirming the fetal SVA mechanism should be sent via secure file transfer for Echo Core Lab review.

Following treatment initiation, it will be possible to document the result of up to 25 prenatal participant encounters in REDCap (from day 1 of treatment to birth or death). Pre-natal participant encounters during

maintenance therapy will occur every 1-3 weeks as clinically indicated/opinion of the Investigator. Information that is captured includes:

- Date of encounter → gestational age at encounter and total days of prenatal treatment
- Patient care: inpatient versus outpatient; methods of maternal-fetal surveillance
- Participant adherence to therapy (first-line therapy only)
- Maternal findings\*: Diagnoses; adverse symptoms (questionnaire); ECG; digoxin level
- Fetal findings\*: diagnoses; rhythm; atrial and ventricular rate; SVA characteristics; date of cardioversion; fetal state; cardiac function, AV regurgitation; umbilical venous flow, FHRM data (log)
- Current medication and treatment recommendations to next encounter
- Rationale of treatment modifications and adherence to Care Maps
- File uploads of new clinically relevant test results#: if relevant new findings, upload maternal 12-lead ECG, M-mode and/or Doppler of current rhythm.

\* = All data will be entered into CRFs and into REDCap. # = images of new, relevant results to be uploaded into REDCap (de-identified) or sent via secure file transfer.

#### PERINATAL.

- Pregnancy and treatment outcomes including date and gestational age at birth or demise
- Number and duration of treatment related maternal hospitalization to birth and adverse outcomes
- Mode of delivery

POSTNATAL. Outcome of live-born babies and their mothers to at least 30 days of corrected postnatal life.

- Newborn:
  - Date and gestational age at birth
  - Weight, height, and head circumference at birth
  - Gender
  - APGAR scores
  - Neonatal complications
  - Neonatal SVA (none, induced or spontaneous) and if applicable SVA mechanism and treatment
  - Neonatal outcome to 30 days
  - Date of discharge from hospital → length of in-hospital care (birth to discharge)
  - Upload: neonatal ECG; SVA tracing if applicable
- Maternal:
  - Delivery complications, management and outcome
  - Date of discharge from hospital → length of in-hospital care (delivery to discharge)
  - Upload: FHRM Questionnaire if completed

**MEDICATION-RELATED PROCEDURES:**

**DRUG SUPPLY.** In accordance with institutional and national regulations, 1<sup>st</sup> line medication to birth or treatment failure will be supplied as specified in site agreements and dispersed as agreed with the pharmacy and in adherence with national regulatory guidelines. There may be brief periods of time when 1<sup>st</sup> line medication will be dispensed from an alternative clinical supply such as during labour and delivery. If this occurs it will be documented but not recorded as a protocol deviation, however attempts should be made to obtain information regarding the lot number and manufacturer. All responsibility for study medication, packaging and labeling is delegated to the Site Investigator as outlined in the Study Agreement. As this is a study of 1<sup>st</sup> line treatment only, once the participant changes therapy to second line medication the medication will be supplied from clinical supply and documentation of accountability will no longer be applicable.

**ACCOUNTABILITY.** An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by an *Investigational Product Accountability Log* kept by the Site Investigator. The amount of study drug dispensed and returned by the subject will be recorded in this log. The responsibility of keeping records of drug accountability will be delegated to the study site. This Accountability Log is only required for 1<sup>st</sup> line study medication for the RCTs.

**COMPLIANCE AND ADHERENCE.** Most mothers with fetal SVA understand the importance of regular drug intake to improve the chances of a normal pregnancy outcome and non-compliance is highly unusual. Nonetheless, participant compliance should be assessed at each visit (for 1<sup>st</sup> line study medication) by inspecting the medication remaining since last dispensing. Adherence rate to treatment since last visit will be calculated as percentage of the prescribed medication that has been taken by the participant since last encounter. In the event that the mother is admitted to hospital and is administered treatment drugs from the hospital pharmacy and not from her personal study medication, self-reporting of dosage will be taken into account when determining adherence. Non-compliance may be suspected if the adherence rate is <80%, is self-reported, digoxin level tests turn out too low or is negative, among others.

**7.9 RCT CENTERS & DURATION.** Requirements of a study site to be considered eligible to participate in the FAST Therapy RCT include:

- The centre provides the primary care of RCT participants from the time of SVA diagnosis to birth or death.
- Neonatal and maternal outcomes to 30 days after birth is ascertained.
- The site investigator/site have the experience, the commitment, and the infrastructure to successfully conduct this research.
- REB approval has been obtained including, if applicable, for affiliated institutions.
- Regulatory approval has been obtained by the study site or, if applicable, the national coordinating center.
- Contracts (data share, legal and financial agreements) have been finalized.

With an anticipated 50 average sized centers and 80% consent rates per RCT, actual study periods are expected to take 1.9 years (SVT without hydrops), 3.8 years (AF without hydrops), and 4.4 years (SVT with hydrops), respectively. This will allow follow-up to 30 days after birth of corrected age of all study participants. Study

completion <5 years will require a minimum of 20 average sized centers in RCT B (SVT without hydrops RCT: 4.7 years), 40 centers in the RCT A (AF without hydrops: 4.7 years), and 45 centers in RCT C (SVT with hydrops: 4.9 years).

**FOLLOW UP STUDIES.** Participant outcomes will be ascertained to 30 days after birth or death. To be able to provide participants with information regarding the outcome of the study and to request their participation in follow-up studies (for example to determine the neurodevelopmental outcome of survivors beyond 1 month of life) we will request the parental permission for electronic contact information (e-mail). The information will be sent to the sponsor via secure file transfer and stored securely at SickKids with only study ID number and e-mail on the form.

**7.10 OUTCOME MEASURES.** Identical outcome measures will be used for RCT and Registry subjects. We expect significant differences in various outcomes among drug regimens based on our preliminary work.<sup>1</sup>

#### **PRIMARY OUTCOME**

- Term delivery ( $\geq 37$  0/7 weeks gestation) with a normal cardiac rhythm (ECG).

#### **SECONDARY OUTCOME**

- Proportion of participants with cardioversion over time
- Proportion of participants with treatment failure
  - Number of participants with treatment failure compared to number of participants with successful treatment.
  - Treatment failure is defined as one of the following:
    1. cross-over to another drug
    2. SVT/AF that persists to birth
    3. preterm birth
    4. death
- Cause of death (prenatal, postnatal)
- Proportion of participants with arrhythmia related death
- Average gestational age at birth
- Birth weight (z-scores)
- Average days of maternal and neonatal hospitalization related to SVA therapy
- Maternal prevalence of pregnancy/treatment-related AEs and outcomes
- Proportion of AEs / adverse outcomes (prenatal, postnatal)

The primary outcome measure is absolute (term delivery without tachyarrhythmia) with no room for interpretation. Secondary outcomes will be the time interval from treatment initiation to the beginning of permanent cardioversion, and once established, the freedom from SVA recurrence on maintenance therapy. Only the final outcome will be considered to classify cases. Cross-over to another agent, fetal demise, development of fetal hydrops, and delivery for SVA will be considered treatment failures. Any recurrence of fetal SVA after

documentation of a normal cardiac rhythm >24 hours by echocardiography will be classified as maintenance treatment failure.

**7.11 STATISTICAL ANALYSES.** All statistical analyses using SAS (SAS Institute, Cary NC) with standard settings will be performed by very experienced statistician from the Cardiovascular Data Management Centre (CVDMC) at SickKids. As a general precept, all 3 RCTs will be analyzed separately. RCT analyses will be performed on an *intention-to-treat basis*, although a separate subgroup analysis will be performed. Descriptive statistics for all study variables, for each study groups separately, will be created using means with standard deviation, median with inter-quartile range, and frequencies as appropriate. Baseline characteristics that should be equally distributed between groups through randomization (age at diagnosis, baseline fetal heart rate, incessant vs. intermittent SVA, maternal age) will be assessed in a test of randomization. The test of randomization will be performed using Fisher’s exact test for categorical variables and Student’s t-test (with Satterthwaite method for variance estimation) for continuous variables.

The **PRIMARY OUTCOME** (proportion of term deliveries without SVA) will be a binary outcome (yes/no). For this type of outcome, the proportion of participants in each therapy arm will be compared using logistic regression models (PROC LOGISTIC) with likelihood ratio test to determine regression model fit, Wald chi-square test from maximum likelihood estimates (Fisher’s scoring technique) to determine statistical significance of the therapy arm and c-statistic from the regression model’s area under the curve (AUC) to measure model accuracy. Effect size estimate and standard error will be converted into odds ratio with 95% confidence (95% CI) limits to facilitate comparisons between the different trials.

**SECONDARY OUTCOME** will also be expressed as binary variables (incl. proportions of participants: requiring 2<sup>nd</sup> line therapy and 3<sup>rd</sup> line therapy; with SVA recurrence on maintenance therapy; delivery without SVA termination; death <1 month; etc.) will be assessed between the different therapy arms in the same way as the primary outcome. For outcomes with time dependent variables (proportion of participants with cardioversion over time; timing of mortality from initiation of therapy), Kaplan-Meier survival curves will be used to depict the event proportion over time for each group. Single phase parametric hazard regression model (PROC PHREG) will be used to compare the 2 therapy arms (with likelihood ratio test to determine regression model fit and maximum likelihood estimates chi-square to determine statistical significance of the therapy arm. Effect size estimate and standard error will be converted into hazard ratio with 95% CI to facilitate comparisons between the different trials. Finally, for outcomes with continuous variables (average gestational age at birth/birth weight z-score; average days of neonatal hospitalization related to SVA therapy), linear regression models using maximum likelihood estimates for parameter estimation will be used (PROC GENMOD: Akaike's information criterion (AIC) criterion to assess regression model fit; Wald chi-square test from maximum likelihood estimates). Effect size estimate and standard error will determine the difference between the therapy arms in the same original units of measurement as the outcome.

**SUB-ANALYSIS** will attempt to determine the factors associated with successful RCT outcomes. To accomplish this, we will use our primary outcome as the dependent variable. Fetal factors (age at diagnosis), SVA characteristics (heart rate; arrhythmia pattern; SVT subtypes) and treatment metrics (agent(s); dose) will be considered as potential independent variables. In a first, all variables will be evaluated separately in univariable



logistic regression models. Those with p-values <0.20 in those models will then be selected for further evaluation in a bootstrap bagging algorithm (500 random resamples). Those variables with high reliability (selected in >50% of the random resamples) will be included in a multivariable logistic regression model (PROC LOGISTIC) with likelihood ratio test to determine regression model fit, Wald chi-square test from maximum likelihood estimates (Fisher's scoring technique) to determine statistical significance of the therapy arm and c-statistic from the regression model's area under the curve (AUC) to measure model accuracy with backward selection of variable (p<0.05 to enter) to obtain a final model. Effect size estimate and standard error will be converted into odds ratio with 95% CI to facilitate comparisons of effect size between the different covariates. This final model would indicate factors associated with greater odds of positive outcome and, providing that analog results are found between the effects of 1<sup>st</sup> line therapy between the 2 models (primary RCT analysis as above and sub-analysis).

**FREQUENCY OF ANALYSIS.** Pre-specified interim analyses of the 3 strata will be performed separately at 50% of enrolment. Each analysis will focus on the primary outcome and safety report including review of between-groups differences and individual review of AEs, other maternal, fetal and infant outcomes, and other safety concerns, if any. All interim analyses will be blinded (with potential un-blinding at the request of the DSMB) as to not influence the final analysis.

**SUBGROUP ANALYSIS.** Additional subgroup analyses will include comparisons with registry participants and impact of tachycardia rates: 1) cardioversion rates over time of RCT participants with SVT and AF  $\pm$  hydrops; and 2) tachycardia rates of cases with persistent SVA at  $\pm$ 1 week of acute therapy (all arms).<sup>1</sup>

## 7.12 QUALITY AND ETHICAL STANDARDS

**QUALITY.** The FAST Therapy Trial will be conducted in accordance with the current approved protocol, GCP guidelines, relevant regulations and standard operating procedures. Regular monitoring will be performed by the FAST Therapy Trial Team as outlined in our *Integrated Quality and Risk Management Plan (IQRMP)*. The Trial Monitor will verify that RCTs are conducted and data is generated, documented and reported in compliance with the protocols, GCP and the applicable regulatory requirements. REDCap files will be monitored regularly by the FAST team for any accidental upload of documents or images containing personal health information. Safety and accuracy of all equipment used in this study, such as ultrasound, ECG, and BP systems, is the responsibility of the study site/department where the equipment is clinically used. All equipment must be properly calibrated and maintained throughout the trial in accordance with the institution's regulations.

**ETHICS.** RCT investigators will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki, and that the trial is conducted in full conformity with relevant regulations and with Guidelines for GCP. The protocol, informed consent forms, participant brochures, and questionnaires will be submitted to the appropriate Research Ethics Committees, and as required to the relevant regulatory authorities, the host and affiliated institutions for written approval. The site investigator will submit and, where necessary, obtain approval from the above parties for amendments to the original approved documents.

The trial staff will ensure that the participants' anonymity is maintained. Each participant will be assigned a unique study ID number to be used in the REDCap database and for communications between the study site and

the trial sponsor. All identifiable documents will be stored securely by the site investigator and will only be accessible by trial staff and authorized personnel.

**REIMBURSEMENTS OF SITES AND SUBJECTS.** Reimbursements of the study site and study participant are to cover expenses related to the preparation and submission of study documents to REB and regulatory authorities, the 1<sup>st</sup> line medication, the collection/reporting of participant data into CRFs and REDCap and fetal heart rate monitors as agreed to by the sponsor. No other participant expenditure will be covered as the care outlined in this protocol is standard of care for these participants and will not require extra-time or extra-visits from the participants.

### **7.13 AGREEMENTS AND POLICIES**

**LEGAL AND FINANCIAL** Financial and legal agreements will be made directly between the Trial Sponsor (Edgar Jaeggi and The Hospital for Sick Children) and the Primary Responsible Site Investigator(s) and his/her Institution(s). In some countries, site agreements and some responsibilities may be delegated to a National Coordinating Site. These Centres will manage and coordinate the national regulatory, and where applicable, the research ethics requirements. This may include delegation of certain on-site monitoring responsibilities as required, from the sponsor to a National Coordinating Site to the extent required by Health Canada. Whether there are requirements for additional monitoring by national regulatory authorities outside Canada will have to be further assessed. Reimbursements will be based on the role of a study site/investigator in the conduct of the trial (National Coordinating Center vs. Participating Center) and the total number of enrolled participants. Reimbursements will reflect a compromise between average costs per RCT participant and the available funds to allow us to successfully conduct and complete the FAST Therapy Trial. The FAST Therapy Trial receives no funds from pharmaceutical companies.

**HEART RATE MONITORS.** We will be able to reimburse costs of up to 100 heart rate Doppler devices to allow fetal heart rate home monitoring of RCT participants at home (1-2 devices per site, depending on expected RCT enrolment rates of the site).

**ACCESS TO SOURCE DOCUMENTS.** The sponsor is obliged to monitor the accuracy and completeness of source documents of a portion of the participants in the trial. To comply with this Health Canada regulation, each trial site agrees upon request to provide *direct access* to a qualified team member of the study sponsor to monitor source documents and other trial related essential documents. Source document review and verification will be randomly chosen but may also be risk-based triggered. Documents may either be faxed to the study Monitor, or be sent via secure file transfer. These documents will be viewed and then securely deleted or destroyed according to SickKids policy on destruction of confidential documents.

## 8. DISSEMINATION OF RESULTS AND PUBLICATION GUIDELINES

Dissemination of results will be decided by the PI and Steering Committee. Publication policy for the FAST Therapy Trial will be included in the study agreement. It is expected that results of the FAST Therapy Trial will be published in several papers by Writing Committees to be determined by the Committee. Individual authorship will be based on the investigator's contribution to a study component (RCTs, Registry; other outcome studies) and journal guidelines of authorship. As per the International Committee of Medical Journal Editors (<http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html>) authorship will be based on these 4 criteria: a) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND b) Drafting the work or revising it critically for important intellectual content; AND c) Final approval of the version to be published; AND d) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Submission of case materials alone does not satisfy the ICMJE authorship requirement. Study Investigators and Collaborators who have significantly contributed but are not included as authors on a manuscript will be listed under "The FAST Therapy Trial Participants" which is a searchable designation in PubMed.

## 9. References

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