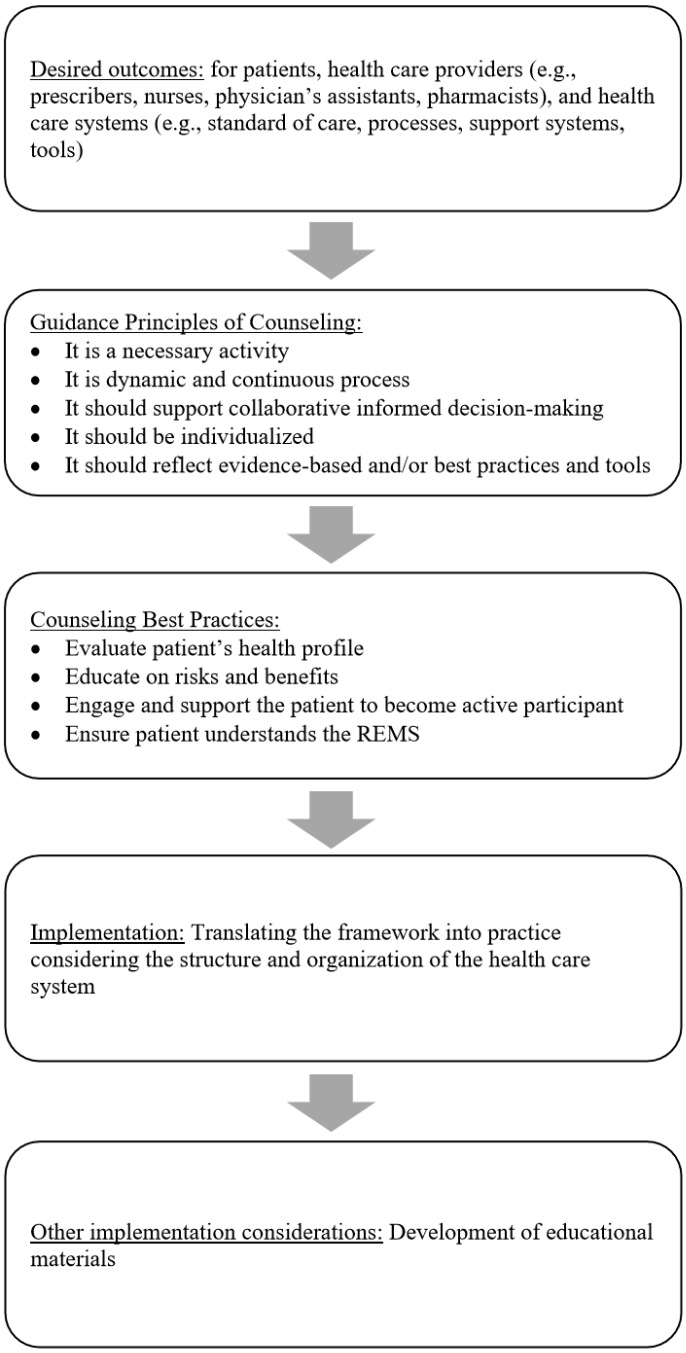
Supplement to: "Turalio® Risk Evaluation and Mitigation Strategy for treatment of tenosynovial giant cell tumor: framework and experience"

Supplemental Figure 1. Modified FDA framework for benefit-risk counseling to patients about drugs with a REMS* [1]



*Adapted from U.S. Food and Drug Administration. A Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS. https://www.fda.gov/media/107591/download. Accessed September 2, 2021.

Supplementary Figure 2. Turalio® REMS Patient Enrollment Form [2]

TURALIO® REMS Patient Enrollment Form

For a patient to receive TURALIO® (pexidartinib), the prescriber must enroll the patient in the TURALIO REMS by completing this form. The patient must review and sign the Patient Attestations section of the form.

Please complete this form online at www.TURALIOREMS.com, fax it to the TURALIO REMS Call Center at 1-833-TRL-REMS or E-mail it to Enroll@TURALIOREMS.com.

Patient Information

First Name:	Middle Initial:	Last Name:
Birthdate (MM/DD/YYYY):		Sex: ☐ Male ☐ Female
Address Line 1:		
Address Line 2:		
City:	State:	ZIP Code:
Phone:	Email:	
Weight: Pounds	Height: Feet	Inches

Race (check one or more): ☐ American Indian or Alaskan Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Other: Specify _____

Is the patient currently taking pexidartinib (i.e., started prior to REMS enrollment)? ☐ Yes ☐ No

If yes: When did patient start pexidartinib? Date (MM/DD/YYYY): _____

If yes: Was this part of a clinical study? ☐ Yes Study Number: _____ Subject ID: _____
☐ No Comment: _____

Prescriber Information

First Name:	Last Name:	NPI #:
Practice/Facility Name (where you see this patient):		
Address Line 1:		
Address Line 2:		
City:	State:	ZIP Code:
Phone:		

Please visit www.turaliorems.com or contact the TURALIO REMS Coordinating Center at 1-833-TURALIO (833-887-2546) to designate up to two additional REMS certified prescribers who can view, edit, and submit REMS paperwork for your TURALIO patients.

Baseline Labs

Assess the patient by obtaining liver tests as stated in the **Prescribing Information**. If Albumin or PT/INR were not obtained, indicate "not applicable." Please provide the results below.

Laboratory Test	Baseline Value (units, reference range)	Date
AST or SGOT		
ALT or SGPT		
GGT		
Total Bilirubin		
Direct Bilirubin		
Alkaline Phosphatase		
Albumin		
PT/INR		

Current Medication (including prescription, non-prescription and herbal or dietary supplements):

☐ Check box if there are no current medications

Medication

Hepatic Medical History:

☐ Check box if this section if there is no hepatic medical history

- ☐ Hepatitis Viral Status
- ☐ Hepatic Cyst
- ☐ Ischemic Hepatitis
- ☐ Alcohol Abuse
- ☐ Family History of Liver Disease
- ☐ Autoimmune Hepatitis
- ☐ Wilson's Disease
- ☐ Drug Abuse
- ☐ Gilbert's syndrome
- ☐ Hypolipoproteinemia
- ☐ Familial Hyperbilirubinemia
- ☐ Anorexia
- ☐ Biliary Tract Disorder
- ☐ Hypertriglyceridemia
- ☐ Cirrhosis
- ☐ Gallbladder Disease/ Gallstones/ Bile Duct Occlusion
- ☐ Diabetes

Prescriber Agreement

I have reviewed and discussed the risks of TURALIO and the requirements of the TURALIO REMS with this patient.

Prescriber Signature:	Date (MM/DD/YYYY):

Patient Attestation

In order to receive TURALIO I must be enrolled in the TURALIO REMS. The TURALIO REMS will collect data to assess the risk of serious liver problems which can be severe and lead to death as described in the **Patient Guide**.

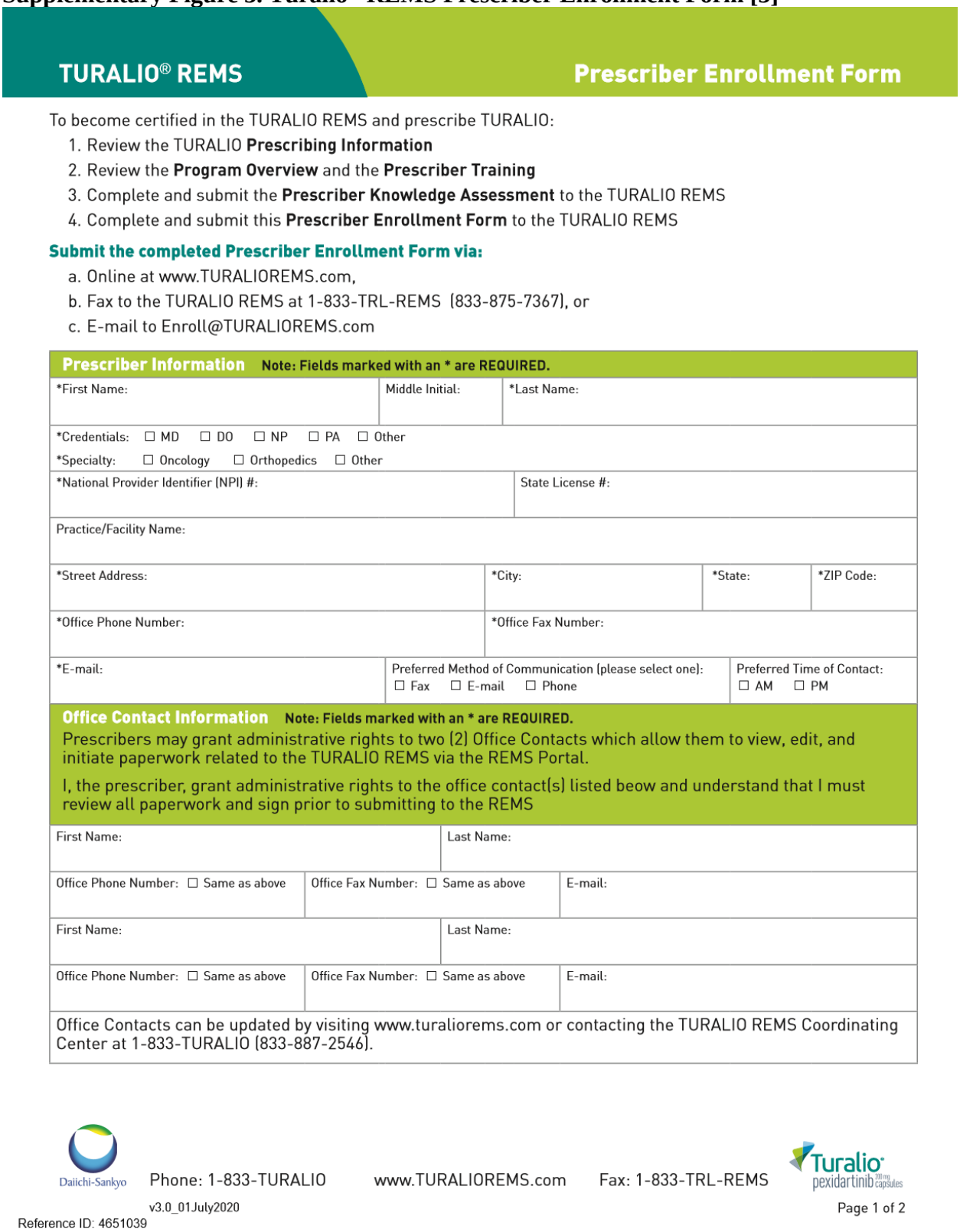
- I agree to enroll in the Patient Registry.
- I agree to review the **Patient Guide**.
- I must get blood tests to test my liver as directed by my healthcare provider.
- I agree to tell my healthcare provider if I have signs and/or symptoms of liver injury.
- My personal information will be shared to enroll me in the Patient Registry so that my health and any liver injury can be evaluated while I am receiving TURALIO.
- Daiichi Sankyo, Inc., and its agents, may contact me or my prescriber by phone, mail or email to manage the TURALIO REMS.
- Daiichi Sankyo, Inc., and its agents, may use and share my personal health information, including lab tests and prescriptions as part of the TURALIO REMS. My information will be protected and will be used to enroll me into and manage the TURALIO REMS. My health information may be shared with the U.S. Food and Drug Administration (FDA) to evaluate the TURALIO REMS.

Patient or Legal Guardian Signature:	Date (MM/DD/YYYY):

Printed Patient or Legal Guardian Name:

Prescribers should always report all adverse events by contacting the REMS at 1-833-TURALIO, Daiichi Sankyo, Inc. at 1-877-4DS-PROD (1-877-437-7763) or FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

Supplementary Figure 3. Turalio® REMS Prescriber Enrollment Form [3]



TURALIO® REMS

Prescriber Enrollment Form

To become certified in the TURALIO REMS and prescribe TURALIO:

1. Review the TURALIO **Prescribing Information**
2. Review the **Program Overview** and the **Prescriber Training**
3. Complete and submit the **Prescriber Knowledge Assessment** to the TURALIO REMS
4. Complete and submit this **Prescriber Enrollment Form** to the TURALIO REMS

Submit the completed Prescriber Enrollment Form via:

a. Online at www.TURALIOREMS.com,
b. Fax to the TURALIO REMS at 1-833-TRL-REMS (833-875-7367), or
c. E-mail to Enroll@TURALIOREMS.com

Prescriber Information **Note: Fields marked with an * are REQUIRED.**

*First Name:	Middle Initial:	*Last Name:

*Credentials: ☐ MD ☐ DO ☐ NP ☐ PA ☐ Other

*Specialty: ☐ Oncology ☐ Orthopedics ☐ Other

*National Provider Identifier (NPI) #:	State License #:

Practice/Facility Name:

*Street Address:	*City:	*State:	*ZIP Code:

*Office Phone Number:	*Office Fax Number:

*E-mail:	Preferred Method of Communication (please select one): ☐ Fax ☐ E-mail ☐ Phone	Preferred Time of Contact: ☐ AM ☐ PM

Office Contact Information **Note: Fields marked with an * are REQUIRED.**

Prescribers may grant administrative rights to two (2) Office Contacts which allow them to view, edit, and initiate paperwork related to the TURALIO REMS via the REMS Portal.

I, the prescriber, grant administrative rights to the office contact(s) listed beow and understand that I must review all paperwork and sign prior to submitting to the REMS

First Name:	Last Name:

Office Phone Number: ☐ Same as above	Office Fax Number: ☐ Same as above	E-mail:

First Name:	Last Name:

Office Phone Number: ☐ Same as above	Office Fax Number: ☐ Same as above	E-mail:

Office Contacts can be updated by visiting www.turaliorems.com or contacting the TURALIO REMS Coordinating Center at 1-833-TURALIO (833-887-2546).

Daiichi-Sankyo Phone: 1-833-TURALIO www.TURALIOREMS.com Fax: 1-833-TRL-REMS Turalio pexidartinib 200 mg capsules

v3.0_01July2020

Page 1 of 2

Reference ID: 4651039

Prescriber Attestations	
By signing this form, I agree TURALIO is only available through the TURALIO REMS and I agree to comply with the following TURALIO REMS requirements: **I have:** • Reviewed the **Prescribing Information**, **Program Overview** and **Prescriber Training**. • Successfully completed the **Prescriber Knowledge Assessment** and submitted it to the TURALIO REMS. **Before treatment initiation and with the first dose of TURALIO:** • I understand that I should counsel the patient on the risk of serious and potentially fatal liver injury, and liver test monitoring at baseline and periodically during treatment. • I must assess the patient by obtaining baseline liver tests. I must submit the results of the assessment on the **Patient Enrollment Form**. • I must enroll patients in the TURALIO REMS by completing and submitting the **Patient Enrollment Form**. **During treatment with TURALIO:** • I must assess the patient by obtaining liver tests weekly for the first 8 weeks, then every 2 weeks for 1 month, then every 3 months and modify the dose of TURALIO as needed in accordance with the **Prescribing Information**. • I must prescribe no more than a 30 days supply for each of the first 3 months of treatment. • I must complete the **Patient Status Form** every month for the first 3 months of treatment, at months 6, 9, and 12 and then every 6 months thereafter while the patient receives TURALIO. **At all times:** • I must report adverse events of serious and potentially fatal liver injury by submitting the **Liver Adverse Event Reporting Form**. • I understand that Daiichi Sankyo, Inc. and/or its agents may contact me by phone, mail or email to provide or obtain additional information related to the REMS program, including details regarding any reported liver adverse events.	
*Prescriber Signature:	*Date:

Supplementary Figure 4. Turalio® REMS Liver Adverse Event Reporting Form [4]

TURALIO® REMS — Liver Adverse Event Reporting Form

Adverse events or laboratory abnormalities suggestive of serious and potentially fatal liver injury must be reported to the REMS.

Adverse events or laboratory abnormalities suggestive of serious and potentially fatal liver injury are:

- **ALT or AST >3xULN and TBIL >2x ULN**
- **ALT or AST >10xULN with or without TBIL elevation**
- **TBIL ≥2xULN (or DBL>1.5xULN) without changes in ALT or AST**
- **ALP >2xULN with GGT>2xULN**
- **Liver Transplantation**
- **Death**

You can complete this form online at www.TURALIOREMS.com, or fax it to the TURALIO REMS Call Center at 1-833-TRL-REMS or call the TURALIO REMS Call Center at 1-833-TURALIO (1-833-887-2546) to provide the information.

Patient Information		
First Name:	Last Name:	Birthdate (MM/DD/YYYY):
Address has not changed: ☐ or update below: Address Line 1:		
Address Line 2:		
City:	State:	ZIP Code:

Prescriber Information		
First Name:	Last Name:	NPI #:
Practice/Facility Name:		
Address has not changed: ☐ or update below: Address Line 1:		
Address Line 2:		
City:	State:	ZIP Code:
Phone		

Liver Adverse Event Reporting

1. What event triggered this report?

2. Report the following labs if they were obtained. If labs were not obtained, indicate "not applicable."

Laboratory Test	Date of tests: _____	Maximum Value and Units	Reference Range Min and Max and Units	Resolved Y/N
AST or SGOT				
ALT or SGPT				
Alkaline Phosphatase				
GGT				
Total Bilirubin				
Direct Bilirubin				
PT/INR				
Albumin (minimum)				
Viral Hepatitis Status		Tests performed, date tested, and results:		

Patient Hepatic Monitoring Information

3. Was a hepatology referral obtained? ☐ Yes ☐ No

4. Were any of the following procedures performed?

Procedure[1]	Yes or No
Liver Ultrasound	☐ Yes ☐ No
Other Imaging of the Liver	☐ Yes ☐ No
Liver Biopsy	☐ Yes ☐ No
ERCP	☐ Yes ☐ No
Hospitalization	☐ Yes ☐ No
Liver Dialysis	☐ Yes ☐ No
Other	☐ Yes ☐ No

[1] If the patient had imaging or the procedure more than once, please provide information about each individual procedure or imaging

5. Medications prescribed to treat event: ☐ Yes ☐ No

6. What is the current status of the liver adverse event (check one)?

- ☐ Resolved, date resolved:_____
- ☐ Ongoing, date of last assessment:_____
- ☐ Resolved with sequelae, describe: _____
- ☐ Liver transplant, date:_____
- ☐ Patient death, date:_____

Signature

Printed Name:	Title:
Signature:	Date (MM/DD/YYYY):

Prescribers should always report all adverse events by contacting the REMS at 1-833-TURALIO, Daiichi Sankyo, Inc. at 1-877-4DS-PROD (1-877-437-7763) or FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

Supplemental Figure 5. Turalio® REMS Pharmacy Enrollment Form [5]

TURALIO™ REMS — Pharmacy Enrollment Form

To become certified in the TURALIO REMS and dispense TURALIO, a pharmacy must designate an Authorized Representative to:

1. Review the **Program Overview**
2. Complete and submit this **Pharmacy Enrollment Form**
3. Oversee implementation and compliance of the TURALIO REMS requirements

Submit the completed Pharmacy Enrollment Form via:

a. Fax to the TURALIO REMS at 1-833-TRL-REMS (833-875-7367), or

b. E-mail to Enroll@TURALIOREMS.com

Authorized Representative Attestations

As the Authorized Pharmacy Representative, I attest that:

- I have reviewed the **Program Overview**.
- I must complete the **Pharmacy Enrollment Form** and submit it to the TURALIO REMS.
- I agree to train all relevant staff involved in dispensing TURALIO using the **Program Overview**.

Before dispensing I will ensure that all pharmacy staff must:

- Obtain authorization to dispense each prescription by contacting the TURALIO REMS to verify the prescriber is certified, and the patient is enrolled and authorized to receive TURALIO.
- Dispense no more than a 30 days supply for each of the first 3 months of treatment.

On behalf of the pharmacy, we will comply with the following TURALIO REMS requirements:

- Report adverse events of serious and potentially fatal liver injury by submitting the **Liver Adverse Event Reporting Form**.
- Not distribute, transfer, loan or sell TURALIO, except to certified dispensers.
- Maintain records documenting staff's completion of training.
- Maintain records that all TURALIO REMS processes and procedures are in place and being followed.
- Maintain and submit dispensing information for all patients.
- Comply with audits carried out by Daiichi Sankyo, Inc. or third party acting on behalf of Daiichi Sankyo, Inc. to ensure that all processes and procedures are in place and are being followed.

Authorized Representative: Please PRINT your name and phone number here.

*Name: _____ (Last) _____ (First) *Phone Number:_____	
*Authorized Representative Signature:	*Date:

Authorized Representative Information **Note: Fields marked with an * are REQUIRED.**		
*First Name:	*Last Name:	Middle Initial:
*Title/Position:		
*Telephone Number:	*Fax Number:	
*E-mail:		
*Preferred Method of Communication (please select one): ☐ Fax ☐ E-mail ☐ Phone		

Pharmacy Information		
Pharmacy Name:		
*Pharmacy Street Address:		
*City:	*State:	*ZIP Code:
*Pharmacy Phone Number:	*Pharmacy Fax Number:	
*Pharmacy National Provider Identifier (NPI) #:		
☐ **If you are certifying more than one pharmacy location, check this box and provide the information on the following page for each site. Use as many forms as necessary.**		
By completing and submitting this form as directed above and receiving certification confirmation, your pharmacy will be certified in the TURALIO REMS. You will receive confirmation of your certification via e-mail.		

Authorized Representative: Please PRINT your name and phone number here.

*Name: _____ _____ *Phone Number:_____
Last First

CERTIFYING MULTIPLE LOCATIONS

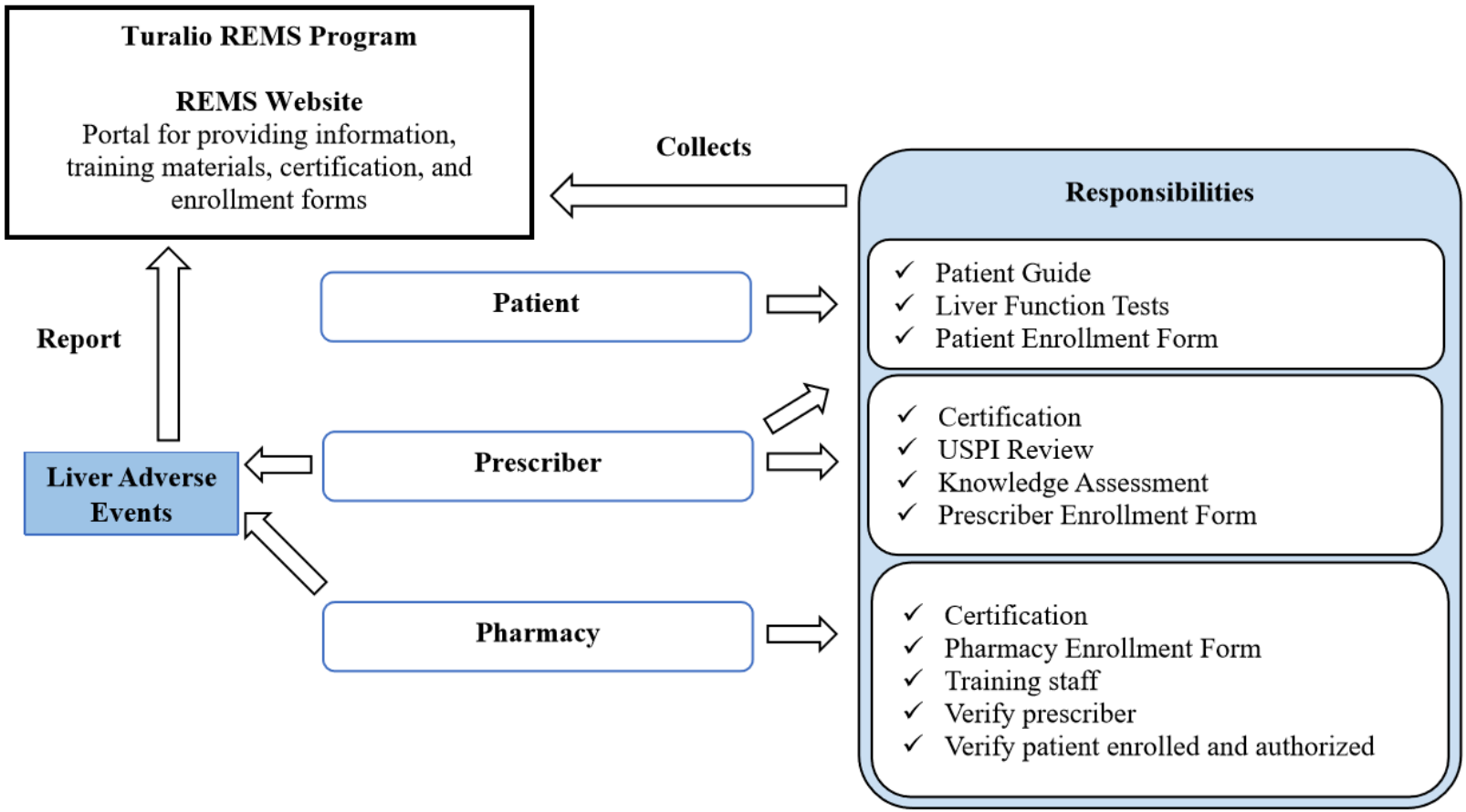
If you are certifying more than one pharmacy location, the following information will need to be provided for each site. Use additional forms as necessary.

Pharmacy Information **Note: Fields marked with an * are REQUIRED.**		
Pharmacy Name:		
*Pharmacy Address:		
*City:	*State:	*ZIP Code:
*Pharmacy Phone Number: Area Code/Telephone Number	*Pharmacy Fax Number:	
*Pharmacy National Provider Identifier (NPI) #:		
Pharmacy Name:		
*Pharmacy Address:		
*City:	*State:	*ZIP Code:
*Pharmacy Phone Number: Area Code/Telephone Number	*Pharmacy Fax Number:	
*Pharmacy National Provider Identifier (NPI) #:		

Authorized Representative: Please PRINT your name and phone number here.

*Name: _____ _____ *Phone Number:_____
Last First

Supplemental Figure 6. Turalio REMS framework



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1. "A Framework for Benefit-Risk Counseling to Patients About Drugs with a REMS." FDA. https://www.fda.gov/media/107591/download. Accessed September 2, 2021.
2. "Turalio® REMS Patient Enrollment Form." Turalio® REMS. 2021. https://www.turaliorems.com/pdfs/TURALIO_REMS_Patient_Enrollment_Form. Accessed September 2, 2021.
3. "Turalio® REMS Prescriber Enrollment Form." Turalio® REMS. 2021. https://www.turaliorems.com/pdfs/TURALIO_REMS_Prescriber_Enrollment_Form. Accessed September 2, 2021.
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5. "Turalio® REMS Pharmacy Enrollment Form." Turalio® REMS. 2021. https://www.turaliorems.com/pdfs/TURALIO_REMS_Pharmacy_Enrollment_Form. Accessed September 2, 2021.