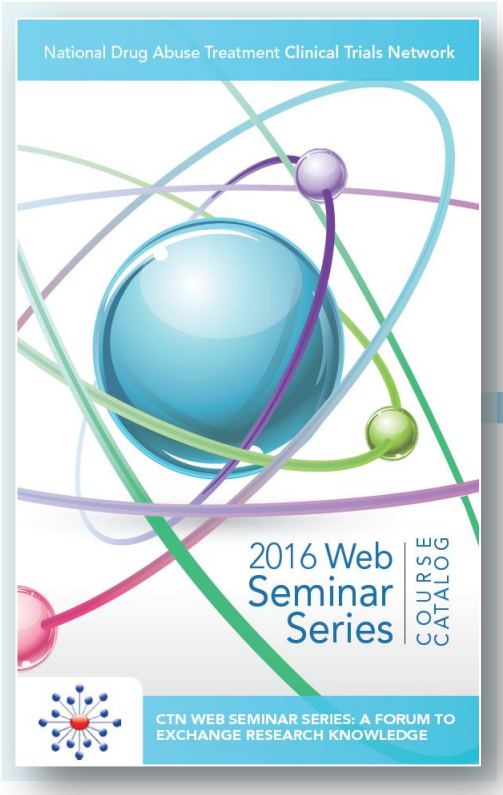

PREPARATION FOR DRUG MANAGEMENT AND ACCOUNTABILITY IN A CTN CLINICAL TRIAL

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CTN WEB SEMINAR SERIES:
A FORUM TO EXCHANGE RESEARCH KNOWLEDGE

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Learning Objectives

- Describe drug management planning and preparation activities.
- Discuss tools for drug inventory and drug accountability tracking.
- Define implementation challenges and quality assurance considerations.

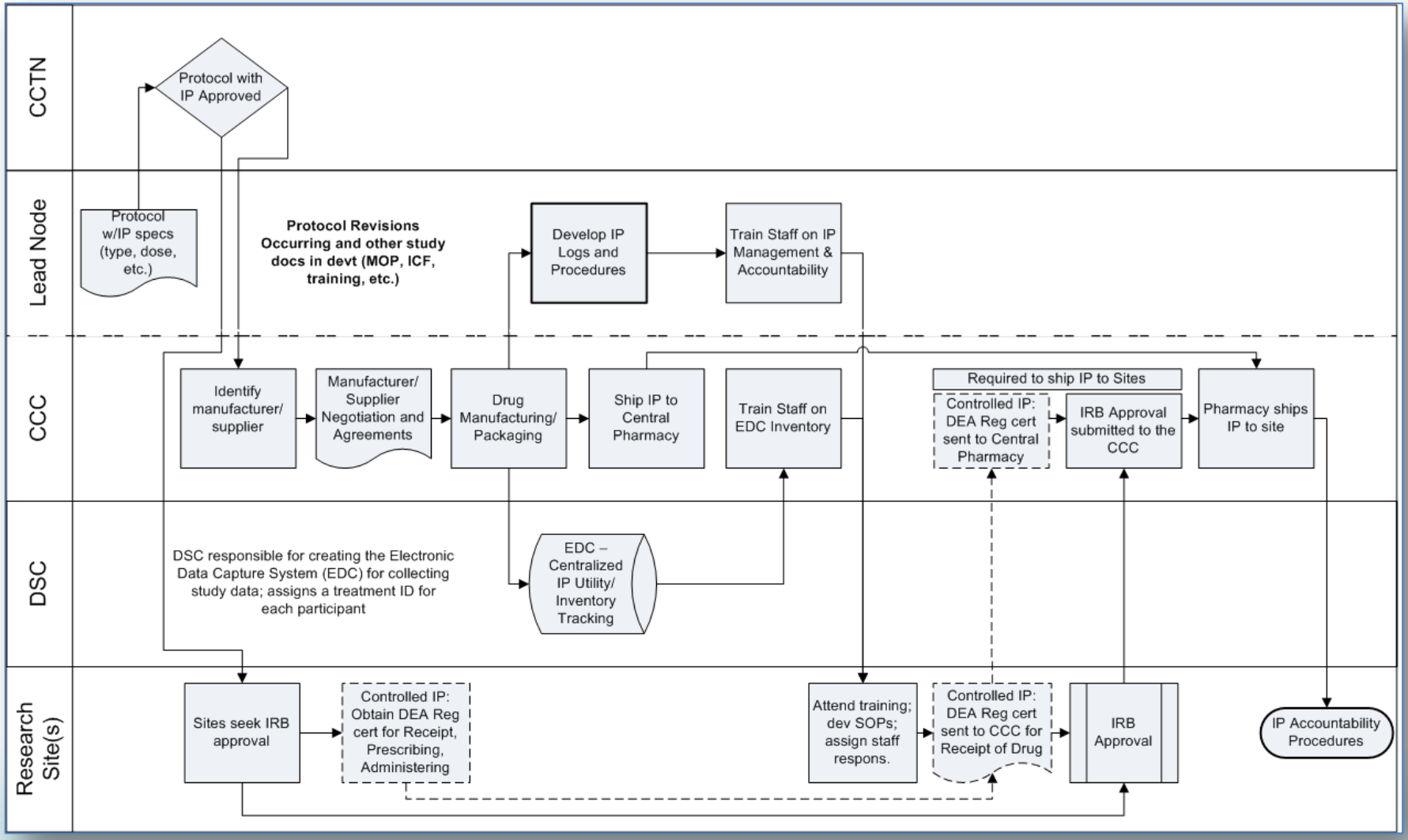
What is Drug Accountability

- More than simply counting pills.
- A process to ensure that research participants receive the correct study drug and dosage, so that effects seen in the study can be linked to the medication administered.
- The FDA has listed drug accountability as number 3 in a list of top 5 pitfalls.

IP Management and Preparation

- Everyone involved in early development, training, and implementation of the IP management and accountability
  - **CCTN** –> guidance, supportive resource
  - **Lead Node** –> procedures and logs for tracking
  - **CCC** –> drug manufacturing and supply with subcontract vendors
  - **DSC** –> electronic data capture system setup/maintenance
  - **Site staff** –> approvals/certification, trained on the procedures and requirements, site level SOPs

IP Management Process Flow in the CTN



GCP Standard and Regulations with IP Management

- GCP guidelines require (GCP (E6) 8)
  - Documentation of IP and trial-related materials shipment.
- Federal regulation (21 CFR 312.62) requires
  - Investigators to maintain adequate records of the disposition of investigational drugs, including dates, quantities, and use by participants [and]…records of receipt
  - Maintain adequate case histories for all participants in studies that involve the use of investigational products
- Retain IP records
  - 2 years after the date a marketing application if approved for the drug for the indication for which is it being investigated by the U.S. Food and Drug Administration (FDA) or for 2 years after the study is discontinued and the FDA is notified
  - CTN requires 3 years documentation retention

Clinical Coordinating Center (CCC) – Prep for IP Manufacturing and Supply

- Manufacturer/Supplier
  - Vendor Identification
  - Negotiation/agreement/funding
  - Packaging/shipping
  - Central Pharmacy Coordination
- IP Analytical Testing and Reporting
- Collect requirements for drug shipping to sites, drug returns, replacement, and destruction

Regulatory Requirements and Supplier Reporting

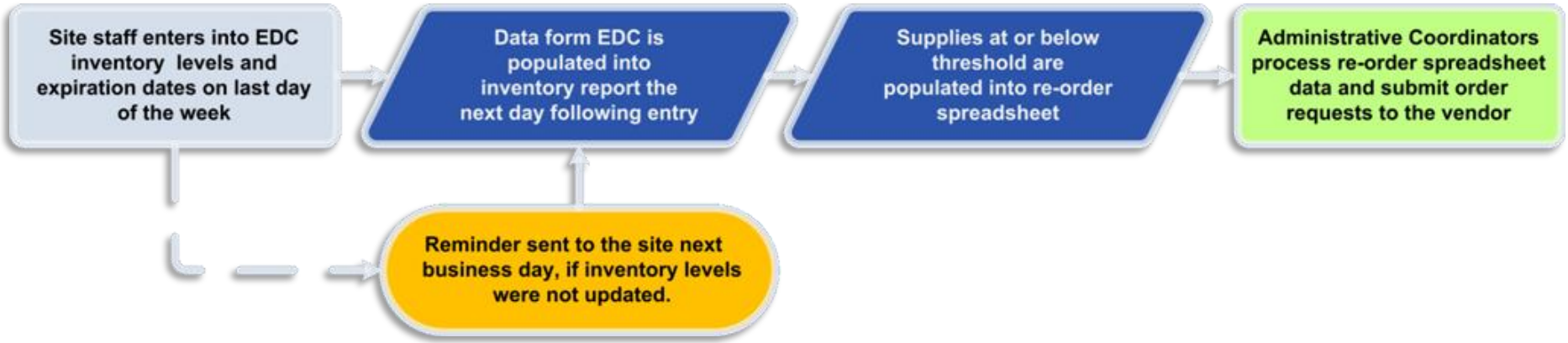
- Sites must provide the CCC with their IRB approval prior to shipment of IP to sites
- For controlled drug (e.g., Buprenorphine or Suboxone), site PI, physician, clinician must provide the DEA registration for Receipt of Drug for the central Pharmacy to ship IP to the site address
- CCC provides reports to regulatory authorities, which may include the IP testing certification or IP accountability logs
- CCC provides additional reports to IP suppliers (reporting requirements vary)

IP Management and Coordination Challenges

- Multisite trials with sites located in various regions
- Determining when to Manufacture and Supply
  - Shelf-life; expiration and replacement of IP
  - Site readiness for study implementation
  - Avoid wasted IP and money
- Maintaining On-Site Adequate Study IP
  - Supply hoarding and last minute requests that occur with manual reordering process
  - Rate fluctuations in enrollment across sites and time

CCC's solutions: A centralized medication and supply inventory tracking and reordering process

- Advantage eClinical or AdvantageEDC^{SM} for inventory tracking
- Programmable reports communicate with the EDC
- 3-step process:



Advanced Features for Drug Utility

- More complex customizable drug utilities can be developed within the electronic randomization system, if needed.
- For example, for blinded medication the system could be set up to send the drug supplier an email containing a list of drug kits to ship to sites.

Strategies for Ensuring Receipt of Drug

- Sites will receive an email from EMINENT indicating that their medication shipment is in route (with relevant tracking numbers provided)

- Upon receipt of medication from EMINENT, sites must :
  - Immediately open carton and inspect and confirm that all listed contents were received in appropriate and usable condition.
  - Fill out and return shipping acknowledgment form to EMINENT via fax provided on shipping form.

Local Procurement of Medications

- Medications that are not study drugs and the research site is responsible for obtaining and re-ordering directly, not through the CCC.
  - For example, naloxone (used for the naloxone challenge in CTN-0051, CTN-0055)

CTN-0051

DEVELOPING AND MAINTAINING IP ACCOUNTABILITY LOGS

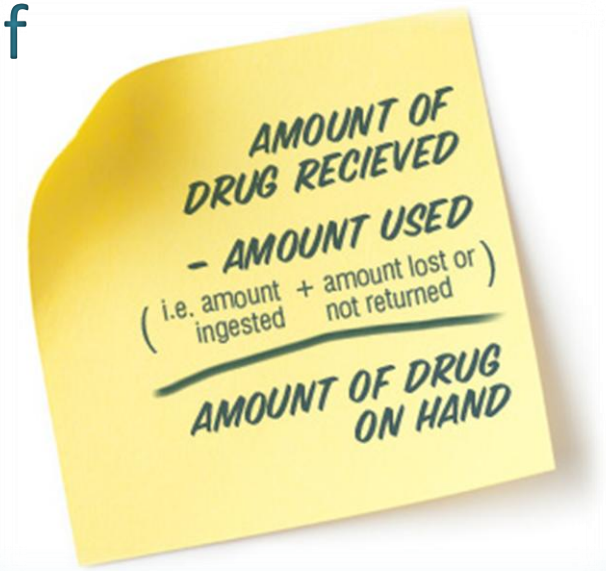
Developing Tools for Site Tracking – Lessons from CTN-0051

- Inventory
- Storage
- Dispensing
- Documentation

CTN-0051 is an open-label study. The medications are Suboxone, a scheduled drug donated by Indivior (formerly Reckitt-Benckiser), Vivitrol, a drug purchased by NIDA for the study, and naloxone, which was to be provided by the sites.

Inventories

- Keep track of how much you have on hand – each medication and dosage.
- Shipments in from EMINENT, central pharmacy
- Prescriptions or other tracking of administration to participants
- Drug returns



Inventories – CTN-0051

CTN-0051 Site Medication Inventory Log – Injectable Naloxone

Only for participants in the Vivitrol (XR-NTX arm); at least 0.8mg/ml must be given

Site Name: _____ Page _____ of _____

RECEIVED INTO INVENTORY				REMOVED FROM INVENTORY					DISPOSITION			
Date Received (mm/dd/yyyy)	Quantity (total ml)	Lot # Exp Date	Received by (initials)	Date Dispensed (mm/dd/yyyy)	Dispensed by (initials)	Amount Dispensed (ml)	Lot #	Assigned to (ppt ID-4 digits)	Disposition (administered, wasted, returned, expired)	Confirmed by (initials/date)	Comments	Inventory Balance (ml)

Inventories – CTN-0051

CTN-0051 Site Medication Inventory Log – Vivitrol (XR-NTX)

Single use kits containing: one 380 mg vial of XR-NTX microspheres, diluent, syringe and needles

Site Name: _____ Page _____ of _____

RECEIVED INTO INVENTORY				REMOVED FROM INVENTORY				DISPOSITION			
Date Received (mm/dd/yyyy)	Quantity (kits)	Lot # Exp Date	Received by (initials)	Date Dispensed (mm/dd/yyyy)	Dispensed by (initials)	Lot #	Assigned to (ppt ID-4 digits)	Disposition (administered, wasted, returned, expired)	Confirmed by (initials/date)	Comments	Inventory Balance (kits)

**Dispensed kits that were <u>not opened</u> may be returned to inventory and assigned to another participant. If the kit seal has been broken, any portion of that kit used, or if kept out of temperature range for more than 7 days, disposition should be noted as "wasted".*

Inventories – CTN-0051

CTN-0051 Site Medication Inventory Log – Suboxone (BUP-NX)

4mg sublingual film

Site Name: _____ Page _____ of _____

RECEIVED INTO INVENTORY				REMOVED FROM INVENTORY					DISPOSITION			
Date Received (mm/dd/yyyy)	Quantity (# 4mg films)	Lot # Exp Date	Received by (initials)	Date Dispensed (mm/dd/yyyy)	Dispensed by (initials)	Amount Dispensed (#films)	Lot #	Assigned to (ppt ID-4 digits)	Disposition (dispensed, returned, expired)	Confirmed by (initials/date)	Comments	Inventory Balance (4mg films)

**Suboxone films that were dispensed from inventory but not given to the participant may be returned to inventory.*
Suboxone films returned by the participant as untaken or missed doses should be returned to the pharmacy for accountability, but should not be returned to the drug inventory.

Inventories – CTN-0051

CTN-0051 Site Medication Waste Log – Suboxone (BUP-NX)

Wasted 4mg and 8mg sublingual film

Site Name: _____ Page _____ of _____

Assigned to (ppt ID-4 digits)	Quantity wasted (# films)				Date returned by ppt (mm/dd/yyyy)	Received by (initials)	Comments	Return balance	
	4mg		8mg						
	# films	Lot #	# films	Lot #				4 mg	8 mg

**Suboxone returned by the participant as untaken or missed doses should be returned to the pharmacy for accountability, but should not be returned to the drug inventory. All Suboxone waste should be documented on this log. All returns for a given participant should be collected and maintained in a baggie until a CCC monitor has completed reconciliation and approved the return to EMINENT.*

Storage

- All 3 medications had different storage requirements
- Locations – drug safe, refrigerator
- Temperature monitoring
- Access/security

Dispensing

- Local SOPs
- Participant medication logs
- Keep a record of:
  - Date
  - Amount
  - Dose
  - Lot #
  - etc.

Dispensing – CTN-0051 PPT Medication Logs

CTN-0051 Participant Medication Log – Vivitrol Arm

Participant ID: (4 digits) _____

Injectable naloxone (naloxone challenge)

Injection number	Administered		Total Dose	Lot #	Route (IV, IM, SC)	Administered by (initials)	Comments
	Date (mm/dd/yyyy)	Time (24hr format)					
1							
2							
3							
4							
5							
6							
7							

The number of naloxone challenges may vary. Participants randomized to Vivitrol must pass a naloxone challenge prior to the initial administration. It may take more than one challenge for a participant to be inducted. It is also possible that a participant may be re-inducted if too much time has elapsed between Vivitrol injections.

Vivitrol (XR-NTX)

Injection number	Administered		Dose Amount	Lot #	Injection Site (Left or Right)	Administered by (initials)	Comments
	Date (mm/dd/yyyy)	Time (24hr format)					
1							
2							
3							
4							
5							
6							
7							

Vivitrol will be administered approximately every 4 weeks, with the final injection occurring no later than week 22. Time between injections must be at least 21 days. In some cases, this may result in a participant receiving a 7th injection.

Dispensing – CTN-0051 PPT Medication Logs

CTN-0051 Participant Medication Log – Suboxone Arm

Participant ID: (4 digits) _____ Page 1 of 2

Suboxone dispensing is expected at study weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 20. Suboxone may be dispensed outside of this schedule (e.g., if a participant misses a dispensing visit) and should be noted in the week in which the dispensing occurs (shaded lines).

Study Week	Date (mm/dd/yyyy)	Prescribed Daily Dose (mg)	Days dose missed (prior week)	# films returned by participant (waste)		Amount Dispensed				Prescribed by (initials)	Comments
				4 mg	8 mg	4 mg films		8 mg films			
						# films	Lot #	# films	Lot #		
0											
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
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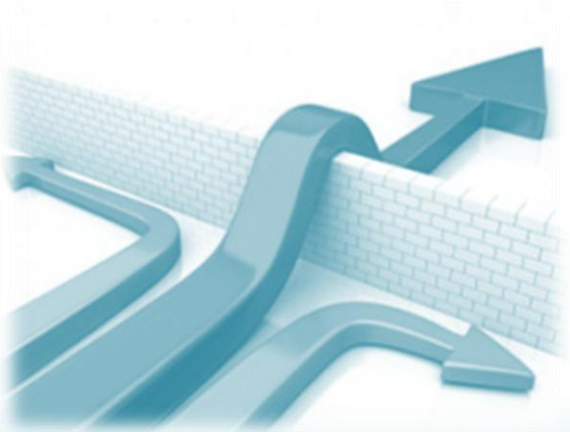
14											
15											
16											

Documentation

- Logs
- Copies of shipping receipts
- Prescriptions
- Signature log(s)
- Training
- Binders

Site Challenges – CTN-0051

- **Open label** – sites already using these medications, extra precautions to keep inventories separate
- **Process** – sites don't necessarily use individual prescriptions in the regular course of business
- **SOPs** – SOPs developed for the study weren't necessarily followed by site staff that were used to doing things differently
- **Staff turnover** – in a long trial, folks trained initially may not still be the ones handling the study drug



Before, during, and at closeout of studies

QUALITY ASSURANCE (QA) IN IP ACCOUNTABILITY

Quality Assurance in IP Accountability

Based on GCP guidelines, site monitors review:

- IP and shipping records to ensure they are on file before the study begins (ICH (E6) GCP 8.2) and accountability procedures are adequate for study conduct (ICH (E6) GCP 6.4.7).
- IP documentation during the trial to ensure that IP has been used according to the protocol (ICH (E6) GCP 8.2.23).
- After trial completion for the final accounting of IP, including drug received, dispensed, returned, and destroyed (ICH (E6) GCP 8.4).

QA of IP On Site

- Sites should ensure that all IP shipment records are accurate
- Reconcile IP accountability logs and ensure storage monitoring logs are current inventory
- Ensure that any excursions are documented appropriately
- Consult the MOP module for IP procedures at closeout, Destruction Instructions, and Site Readiness for Closeout Checklist

QA of IP On Site

- CCC Monitor to work with site staff on drug return
- Site staff required to complete the **Agent Return (IP) Form**

Guidance for Medication Return for CTN-0051

CTN-0051 BUP-NX Medication Return

BUP-NX (provided as Suboxone® sublingual film, 4mg and 8mg) that is returned by a participant may not be re-issued for use. All unused study medication will be logged into a cumulative inventory which tracks the return of study medication. All damaged, returned, expired or unused study medication must be reconciled by the NIDA CCC site monitor before the medication can be sent to the central distributor or a reverse distributor for destruction, as per the protocol (Section 8.6.4 Used/Unused Medication).

During an on-site monitoring visit, the NIDA CCC site monitor will perform drug reconciliation. The monitor, along with a site staff member, will then complete the Agent Return Form. The site staff member who is observing the reconciliation and consolidation process and the monitor who is performing the process must sign and date the form.

After the form is completed, make two photocopies of the Agent Return Form. Place the original inside the package (to be returned to EMINENT), give one copy to the monitor, and keep the second copy in the site records.

The monitor will provide all the necessary supplies (envelopes, baggies, airbills) needed to return study medication.

EMINENT SERVICES CORPORATION

The EMMES Corporation - NIDA (Protocol# CTN-0051)

AGENT RETURN FORM

The Agents listed below were returned by: _____

Site Name: _____

Site#: _____

Address: _____

INSTRUCTIONS FOR INVESTIGATOR

1. Type or print clearly all information-one item per line. Fill in all sections.
2. **DO NOT** mark in the shaded area.
3. Sign and date list.
4. Pack the agents well to minimize breakage and leakage.
5. Enclose the completed list with the agents and return to:

The EMMES Corporation - NIDA (Protocol# CTN-0051) (0046)
c/o EMINENT Services Corporation
7495 New Technology Way
Frederick, MD 21703
Phone# 240-629-1972

Agent Name	Unit	Status (Used / Unused)	Quantity	Lot #	For EMINENT Use Only	
					Rec. No.	Received by: Date:
Suboxone® (buprenorphine and naloxone) sublingual film, 4 mg/1 mg	1 Film Pouch	Unused				
Suboxone® (buprenorphine and naloxone) sublingual film, 8 mg/2 mg	1 Film Pouch	Unused				Checked by: Date:

To be completed by site
Individual preparing this list:
(if other than the investigator)

Name (Site Staff) _____ Title _____

Signature and Date (Site Staff) _____ Telephone No. _____

Name (CCC Monitor) _____ Title _____

Signature and Date (CCC Monitor) _____ Telephone No. _____

Comments: _____

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Quality Assurance of IP Records after Closeout

- Address any outstanding issues and action items related to the IP records
- Prepare the IP records for long term storage
- Answer any questions the CCC may direct to the site in the process of reconciling drug logs

Additional IP Accountability after Study Closeout

- All drug logs supplied to Regulatory entities and suppliers
  - Sites to provide final drug logs to CCC for summary reporting
- CCC to do overall Reconciliation (between distribution, receipt, administration, disposition, loss, destruction records)
- IP Disposition Procedures
  - IP returned to the central pharmacy for destruction or storage, or
  - Sites may donate the remaining IP (if not expired) per local and institutional policy

QA – Challenges in IP Accountability

- Long visit intervals can lead to participants missing doses or misplacing medication
- Incomplete logs lead to unaccounted medication
- Missing information on logs can lead to impossible reconciliations
- Omission of transfer documentation (e.g., shipping receipts) can lead to unaccounted medication

WRAP UP

Take away messages…

- Drug Management and Accountability is required based on GCP guidelines and other regulatory standards
- Everyone is involved, from the sponsor to the Lead Node, CCC/DSC, and the research site staff
- Drug management has a lot of moving parts and can be complex
- Plan for drug accountability early in the development phase of the study; effort up front may save time in the end
- Don’t remake the wheel; there are tools out there that can be used when creating drug logs for your study

References

- ICH Guideline for Good Clinical Practice E6(R1). (1996). Retrieved from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html.
- CFR - Code of Federal Regulations Title 21. (2016). Retrieved from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62.

Questions / Comments

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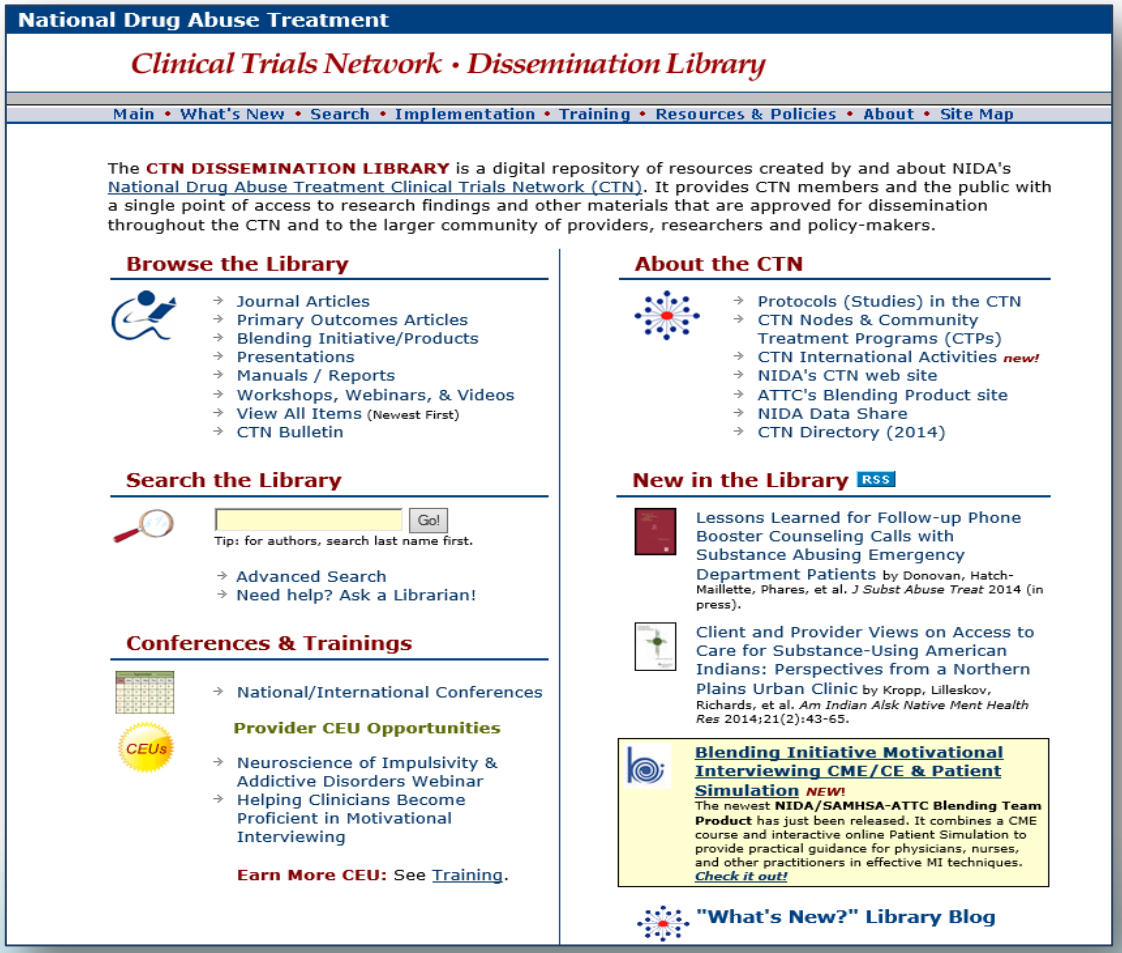

Next Topic…

PERCEPTIONS OF HARM AND ADDICTION OF SNUS

Wednesday, November 30, 2016
at 1:00 pm ET

THANK YOU FOR YOUR PARTICIPATION