ANRS Méthaville trial

Initialization of methadone in primary care: a phase III randomized trial

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Background (1)

Consensus conference (2004) :

The main recommendation was the need for expanding access to opioïd substitution treatment (OST) for opioïd dependent individuals by making possible the initialization of methadone in primary care.

Drug users' needs:

Expanding access to OST by increasing the spectrum of modalities for delivery and entry points: less stigmatizing sites used as entry points while assuring comprehensive care.

Problems of access to methadone:

Geographic heterogeneity and problems of stigmatization of patients in center for drug dependence (CSST).

Experiences outside France:

Role of the model of care to council access and safety.

Background (2)

Since the introduction of OST and needle exchange programs :

- OST coverage is now 70%.
- Dramatic decrease of overdose deaths, drug-related crimes and HIV prevalence among drug users (from 40% (1996) to 11% (2004).

However, HCV prévalence among drug users remains stable (60%) (BEH, 2006-Coquelicot 2004)

⇒ **Need to increase OST coverage to engage recent injectors in OST care**

Background （3）

Individual benefits of methadone are well-known :

1. Among individuals who have access to methadone, a decrease of injecting and sexual behaviours at risk together with a reduction of HIV seroconversion is observed (Sorensen & Copeland, 2000).

2. Results from the Amsterdam cohort show that access to methadone and NEP has an impact on HCV seroconversion (Van den Berg, 2007).

The risk of overdose

Despite these benefits, patients receiving methadone are at increased risk of overdose:

1. Compared with the general population, patients on methadone have a RR=4.6 of dying from overdose (Maxwell, 2005).
2. The great majority of overdose deaths occur in the first two weeks.
3. Factors associated with death from overdose are: prescription of a low dose of methadone, younger age, poly-drug use, elevated alcohol consumption, recent experience of prison.

Main objective of the trial

To show the equivalence between MT in primary care vs. MT in drug center in reducing the risk of HCV transmission

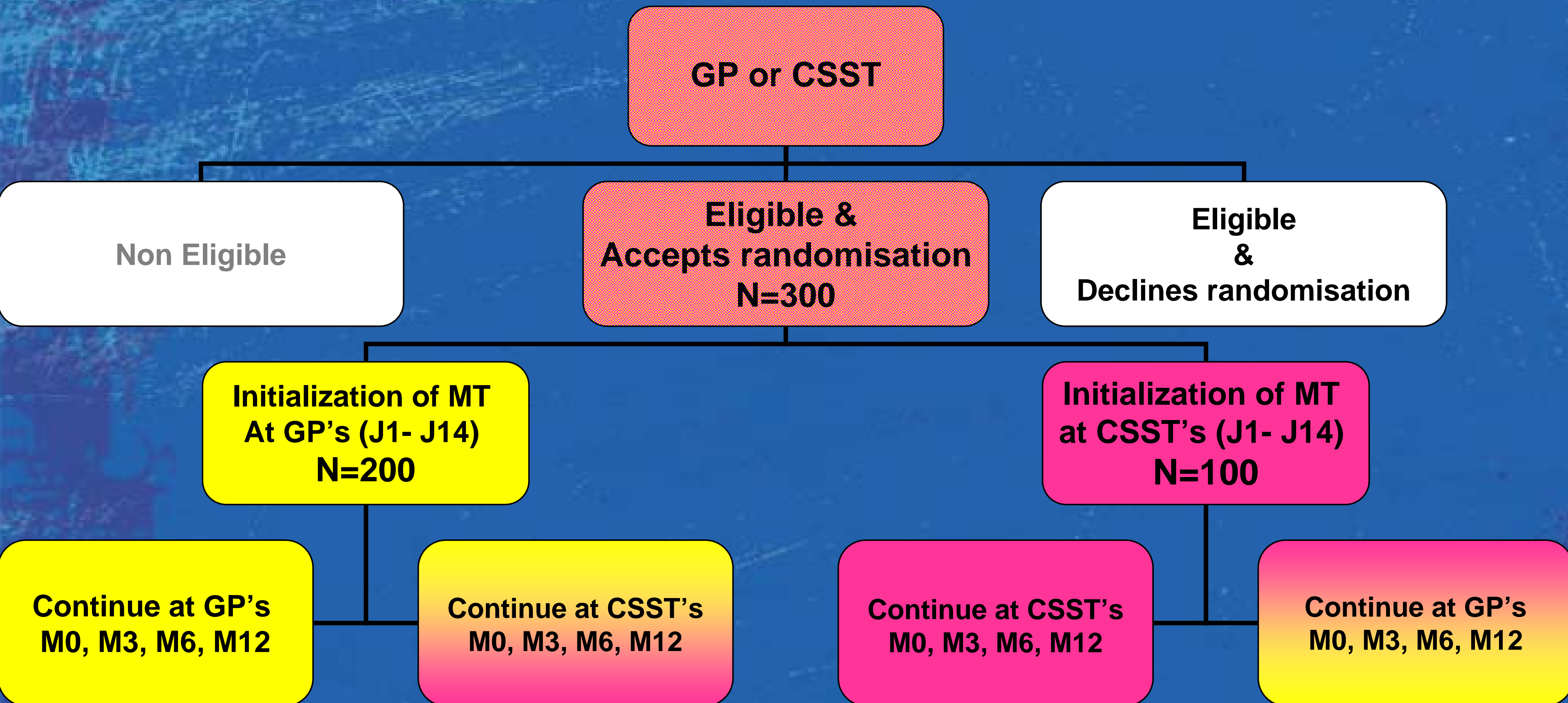
2 main secondary objectives

1. To compare other practices at risk of HCV transmission over time

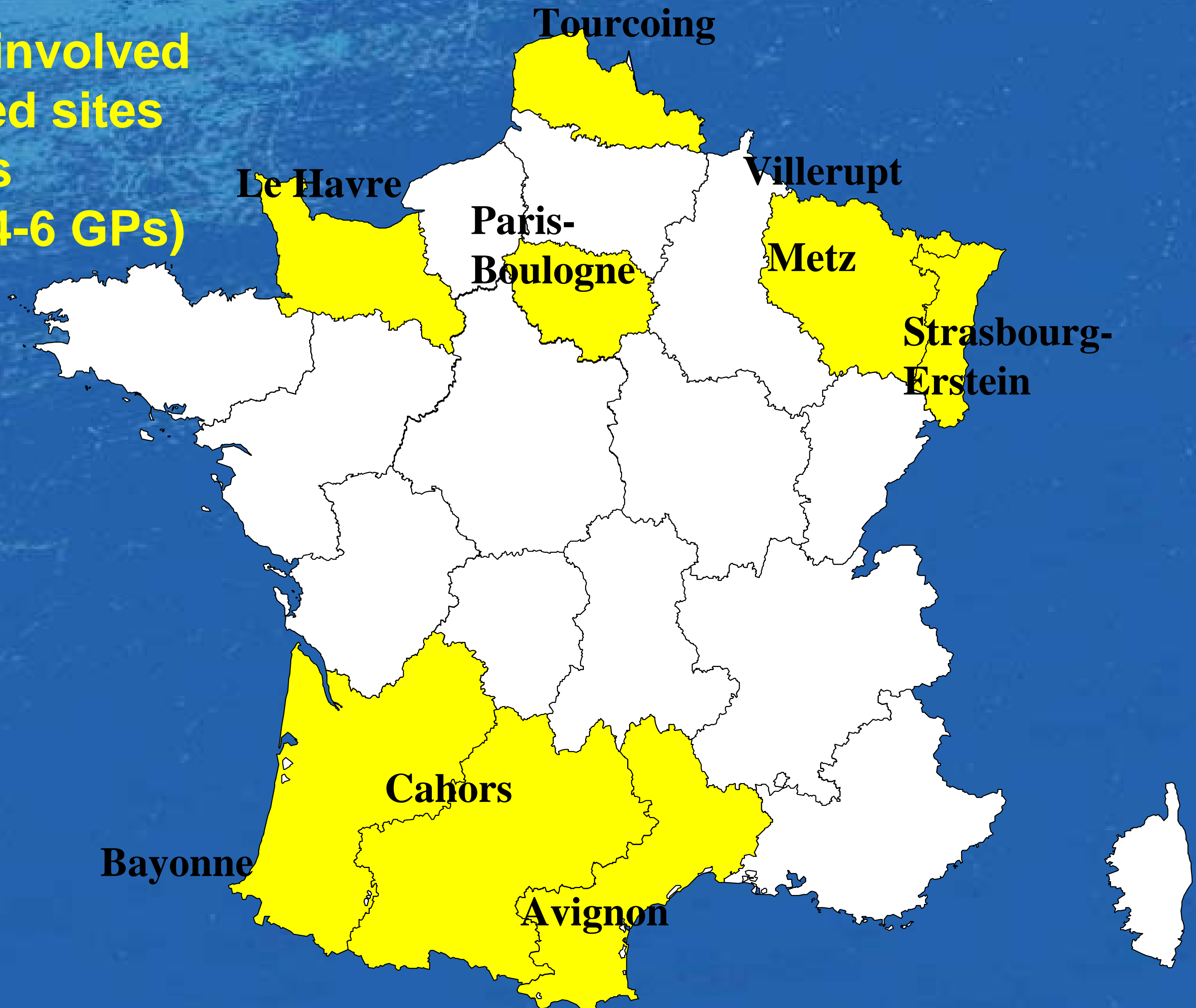
2. To compare the effectiveness of methadone in terms of

   - Adherence
   - Other addictive behaviors
   - Social insertion
   - Quality of life (general, symptoms, pain and psychiatric co-morbidity)
   - Criminal acts
   - Satisfaction and cost-effectiveness

Methaville: design of the trial



10 towns involved
13 matched sites
CSST-GPs
(1 CSST: 4-6 GPs)



Primary and secondary outcomes

Primary outcomes

Daily injection after 1 year of MT

Secondary outcomes

1. Risk transmission practices for HCV over time, HCV seroconversion(?)
2. Effectiveness of methadone in primary care
   - Adherence to MT (retention, generally follow prescription, addictive behaviors)
   - Addictive behaviors
   - Improvement in quality of life, social insertion, psychiatric symptoms and other co-morbidities
   - Decrease of drug-related crimes
   - Costs -effectiveness

Model of care

- Shared-care model : GPs should work within a drug user care network and/or a CSST and have documented experience of care for drug users.

- All prescribing physicians should attend a training program and follow the guidelines for the trial when prescribing MT to patients included in the trial.

- Surveillance system for fatal and non fatal overdoses (severe adverse effects from post-marketing surveillance - CEIP PACA).

Inclusion criteria

1. Drug users dependent on opioïds, aged more than 18 years, who have not been prescribed methadone for 1 months.

2. Drug users aged more than 18 years in buprenorphine treatment failure ("switchers").

Exclusion criteria

in drug labelling (DL)- out DL

1. Patients with contra–indication for MT
2. Patients already receiving antagonist or partial agonist drugs (naltrexone, pentazocine, nalbuphine)
3. Patients receiving sultopride.

4. Patients living in an “irregular” situation.
5. Patients “co-dependent” on both benzodiazepines and alcohol (as screened by MINI).
6. Pregnant women
7. Individual not reachable by phone.
8. Patients aged less than 18 ans.

Statistical considerations: sample size

To test the equivalence of the proportion of daily injectors after 1 year since MT initiation:

- 15% patients inject daily after 1 year (Hutchinson 2000)
- An acceptable difference between arms = 15%
- A confidence level = 95%
- A power= 80%
- A GPs/ CSST ratio= 2: 1

☞ 158 individuals after 1 year et 300 to be enrolled

Data Collection

	M-2	M0	J1-J7	J8-J14	M3	M6	M12
Medical questionnaire (pre-selection)	X						
Informed consent		X					
Urine screening		X			X	X	X
Medical questionnaire (enrolment)		X					
Medical questionnaire (follow-up)			X	X	X	X	X
Pharmacist questionnaire (enrolment)		X					
Pharmacist questionnaire (follow up)			X	X			
Patient's interview		X			X	X	X

Legal barriers

- CPP (Committee for the Protection of People) ethical folder: problems when adapting the intervention trial to the criteria of a phase III clinical trial
- CNIL fold for confidentiality of information
- Agreement from physicians
- Agreement from pharmacists
- Dispensation for pharmacists to deliver clinical lots (a standard procedure)
- Problems for the traceability of lots of a narcotic

Administrative barriers

- Convention with the CEIP PACA for matching data from the post-marketing surveillance of fatal and non fatal overdoses
- Agreement from the National Health Insurance in order to cover the costs of the prescribed treatments and other related charges
- Covering the fees for patients without complementary health insurance

Operational barriers

- Monitoring medical data using a system on line: set up of a virtual private network (VPN) with updated information in real time
- Training for physicians
- Management of patients changing arms or prescribing physician
- Phone interview (CASI)

Impact on public health

- Guidelines for methadone prescription and dispensation
- Experience with interventional research for prevention and methodological-related issues: assure internal and external validity while accounting for the drop-out process and the selection bias.
- Results could be useful for countries with high prevalence of HIV and HCV among drug users and that urgently need to start or expand access to OST