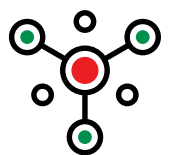




# Reducing fatal opioid overdose

Preventing and treating heroin overdose:  
the Villa Maraini Foundation experience

**RED CROSS AND RED CRESCENT  
PARTNERSHIP ON SUBSTANCE ABUSE**



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# Audience for this publication

This document has been developed by the International Red Cross and Red Crescent Partnership on Substance Abuse, and includes recommendations as to whether and how a National Red Cross or Red Crescent Society should get involved in contributing to the prevention of opioid abuse using naloxone. It includes the experience of the Villa Maraini Foundation programme and its achievements in this area.

The publication should be considered in conjunction with other relevant World Health Organization (WHO) and United Nations Office on Drugs and Crime (UNODC) publications. See the references and the Further reading section.

# Glossary/acronyms and abbreviations

Glossary items are found in **bold** in the text.

Agonist	A chemical that produces a biological response
Analgesia	Inability to feel pain
Antagonist	A chemical that blocks the action of the agonist
Bioavailability	The proportion of the drug able to have an active effect
Crackles	Abnormal sounds from the lung, such as clicking or rattling
Cyanosis	Bluish discolouration of the skin
Half-life	The time required for the concentration (e.g. of a drug) in the body to decrease by half
Hypoxia	Insufficient oxygen getting to the tissues
Metabolite	Substance formed in, or necessary for metabolism to occur
Metabolism	The chemical processes that occur within a living organism in order to maintain life
Mylohyoid muscle	A muscular sling that forms part of the floor of the mouth
Pathogenesis	The way a disease develops
Phlebitis	Inflammation of a vein
Receptor	Molecules able to receive chemical signals. Opioids bind to their receptors in the central and peripheral nervous system in order to elicit their specific biological response
Thrombosis	Clotting of the blood in part of the circulatory system
Titrate	To measure vital functions continuously and adjust dose accordingly
A&E	Accident and Emergency Department
ALS	Advanced Life Support
BLS	Basic Life Support
BLS-D	Basic Life Support and Defibrillation
CNS	Central nervous system
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
i.v.	Intravenous
UNODC	United Nations Office on Drugs and Crime
VMF	Villa Maraini Foundation
WHO	World Health Organization

# Reducing fatal opioid overdose

## Prevention, treatment and harm reduction strategies

### Foreword: International Red Cross and Red Crescent Partnership on Substance Abuse

The IFRC, the Italian Red Cross and the Villa Maraini Foundation, in response to high levels of drug use and related problems globally, have established a tripartite international partnership on substance abuse. The three institutions join efforts to maximize and leverage the expertise of each partner to support the Red Cross Red Crescent to expand comprehensive approaches to drug abuse, with a focus on harm reduction and the fight against stigma and social exclusion. Key activities directly contribute to support the IFRC *Strategy 2020*, the Strategic Operational Framework for Health (SoF) and the process of building resilience. Support is given to National Societies to enhance activities addressing and meeting the basic needs of communities suffering from drug abuse, as well as accessing health and education, eliminating health inequities and advocating for the respect of human rights.

In 2005, the Red Cross Red Crescent, led by the Italian Red Cross, initiated a strong advocacy initiative to promote a humanitarian drug policy in response to the health disaster caused by drug use and drug addiction. The document called the Rome Consensus, signed by over 120 National Societies, provides a framework that clearly lays out health principles and practices, information and research on drug consumption issues and best practices in drug policy responses, and assists National Societies in implementing effective actions and programmes within their communities.

In 2011, the Governing Board meeting adopted a special decision on substance abuse to reinforce the Red Cross Red Crescent response to drug-related issues. In 2012, IFRC signed a partnership agreement with UNODC to address the issues of drug use and related harm at the community level. Today a number of National Red Cross and Red Crescent Societies worldwide have already initiated harm reduction strategies in collaboration with governments and other multilateral and non-governmental organizations. Activities support drug users and advocate for the acceptance, introduction and maintenance of harm reduction programmes. Harm reduction projects demonstrate encouraging results in addressing the problem. Since 2004, Italian Red Cross and IFRC, in collaboration with Villa Maraini, have been offering training services to National Societies and other partners.

The Partnership strongly encourages National Red Cross or Red Crescent Societies around the world to take note of the following set of recommendations put forward to counter the threat of fatal opioid overdose: a severe threat to public health everywhere. In addition, the document which accompanies these recommendations gives background information on heroin overdose and one specific harm reduction strategy that has proved very successful. This is the Italian Red Cross Villa Maraini programme to treat heroin overdose on the street.

**Massimo Barra**

*Chairman of the Red Cross Red Crescent  
Partnership on Substance Abuse*

## Reducing opioid-related deaths

The opioid overdose epidemic has become one of the greatest threats to public health all around the world. Globally, UNODC estimates that of more than 207,000 annual drug-related deaths worldwide, most of those are caused by overdose<sup>a</sup>. A recent official report of the US National Institute on Drug Abuse estimated 64,000 overdose deaths in the United States alone during 2016<sup>b</sup>.

The most recent WHO guidelines<sup>c</sup> aim to reduce the number of opioid-related deaths globally. The guidelines recommend that countries **expand naloxone access for persons** likely to witness an overdose in their community, such as friends, family members and partners of people who use drugs, along with social workers. In most countries, naloxone is currently accessible only through hospitals and ambulance crews, who may not manage to provide help to people who need it fast enough. Naloxone has been used in the management of opioid overdose for more than 40 years. It is a safe drug with a low risk of serious side effects. According to the guidelines, any adult capable of learning basic life support can also learn to recognize an opioid overdose and administer naloxone in time to save lives.

The **International Red Cross and Red Crescent Movement**, in line with its strategy objectives ‘*saving lives, changing minds*’ should contribute to the development and implementation of a variety of strategies to reduce fatal overdoses and save lives through prevention, treatment and harm reduction strategies, as already recommended by the Group of Experts on Drug Abuse of Red Cross Red Crescent in 1980<sup>d</sup>.

Through community-based action, capacity building for addressing health challenges in acute or chronic humanitarian situations and resilience building of affected communities and people, the International Red Cross and Red Crescent Movement has significant experience in community mobilization, access to health and social services and protection for people left behind. This experience has contributed significantly in many countries to address the problems of drug users in communities by improving harm reduction services. To strengthen drug abuse prevention and response, several health workforce initiatives have been launched aiming to create or mobilize multi-task community health workers (CHW), integrated in the systems for health strengthening, and to ensure community engagement and task shifting between the CHWs and other health cadres. The Red Cross Red Crescent Movement is an important partner in massively scaling up response to the problem, specifically to prevent and treat overdose – harnessing the skills and experiences of the volunteers in the National Red Cross or Red Crescent Societies.

Many strategies are focused on primary prevention and increased access to effective treatment, although the past decade has seen an exponential increase in harm reduction initiatives. In many countries, the policy changes are designed to increase assistance during a witnessed overdose, while in other countries there are still many legal and cultural barriers to implement a humanitarian approach to this phenomenon. Increased public and political awareness of this issue have facilitated widespread implementation of several initiatives, including improved distribution of naloxone, based on effective and evidence-based activities, as recorded in the accompanying document regarding the direct experience of the **Italian Red Cross Villa Maraini Foundation**, the Hub of the IFRC international Partnership on Substance Abuse.

<sup>a</sup> [www.unodc.org/doc/wdr2016/WORLD\\_DRUG\\_REPORT\\_2016\\_web.pdf](http://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf)

<sup>b</sup> [www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates](http://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates)

<sup>c</sup> [www.who.int/substance\\_abuse/publications/management\\_opioid\\_overdose/en/](http://www.who.int/substance_abuse/publications/management_opioid_overdose/en/)

<sup>d</sup> [www.massimobarra.it/images/ARTICOLI/2014/30\\_years\\_of\\_naloxone.pdf](http://www.massimobarra.it/images/ARTICOLI/2014/30_years_of_naloxone.pdf)

## Recommendations

National Red Cross and Red Crescent Societies must promote the expansion of access to and use of naloxone – a non-addictive, life-saving drug that can reverse the effects of an opioid overdose when administered in time.

### Access to naloxone can be expanded through:

- Standing orders at pharmacies
- Availability through local, community-based organizations
- Access and use by law enforcement officials
- Training for basic emergency, medical and community health service staff on how to administer the drug
- Training of drug users, friends, family members

### Health authorities should:

- Recognize the right to health and access to naloxone life-saving drug
- Develop an enabling policy and legal framework
- Assess health system preparedness to meet the needs of people who may be at risk of overdose
- Ensure political commitment and guarantee entitlement and access of people to harm reduction services
- Ensure the services are drug user-friendly and sensitive
- Optimize service provision, especially through primary health care, including effective prevention and care
- Follow internationally recognized policies
- Understand and accept the role of National Red Cross or Red Crescent Societies in the country in the area of health/harm reduction

### The National Society should:

- Have dedicated professional staff and recruit volunteers to work closely with health institutions and/or highly motivated and trained volunteers
- Treat all persons with dignity and respect and support for self-reliance
- Include harm reduction component in Red Cross Red Crescent community-based health programmes, including training in overdose prevention
- Include overdose management in basic first aid training curricula
- Respond to people in distress in a humane and supportive way
- Provide information about services, supports and legal rights and obligations
- Urge governments throughout the world to respect the rights of people who use drugs
- Cooperate with other non-governmental organizations in the field



**Specific focus areas in Red Cross Red Crescent programmes:**

- Prevent drug-related deaths according to national circumstances as, for example in the case of opiates, by providing access to authorised pharmaceutical-dosage forms of medicinal products containing naloxone which have been specifically created to treat opioid overdose symptoms by trained community workers and volunteers in the absence of medical professionals.
- Scale up the availability, coverage and access to risk and harm reduction services, e.g. needle and syringe exchange programmes, opioid substitution treatment and opioid overdose management programmes. This will decrease the negative consequences of drug use and prevent and reduce the number of direct and indirect drug-related deaths and infectious blood-borne diseases (in accordance with the WHO recommendation on the comprehensive package of health services for people who inject drugs<sup>6</sup>).
- Provide naloxone training for drug users themselves, friends, families and community workers as a necessary prerequisite for safe take-home programmes, peer-based interventions, outreach treatment programmes, Hepatitis C (HCV) treatment, pill testing, quick-testing for HIV and HCV, in accordance with national legislation. Include in Red Cross Red Crescent first aid training curricula prevention and first aid during overdose. This will mean acquainting trainees with basic life-saving knowledge and skills to ensure effective response should overdose occur.
- Identify and overcome barriers in detection and access to treatment for HIV and HCV among people who inject drugs, including prisoners and other key populations.
- Include, in prison projects, services for drug users: opioid substitution treatment, naloxone programmes, and if applicable needle and syringe exchange programmes in accordance with national legislation and prevention and management of HIV, Hepatitis B, Hepatitis C and TB.
- Provide continuity of care for prisoners upon release, with particular emphasis on avoiding drug overdoses.

# Preventing and treating heroin overdose

## 1. Introduction: the Villa Maraini Foundation programme



The Villa Maraini Foundation, part of the Italian Red Cross, offers a number of facilities and services for the care and rehabilitation of people who have become dependent on drugs. Services include a night centre for the homeless, a unit offering support to drug users infected with HIV/AIDS, a training centre for staff and an emergency unit which runs “street units”, that is, mobile units often staffed by former drug users who are trained to contact and assist drug users in the places where they use drugs: in the streets, in poor neighbourhoods, in railway stations, tunnels, waste ground, etc.

In 1976 the Italian Red Cross inaugurated the Villa Maraini Foundation with the aim of providing a safe haven for individuals with problematic drug use. In agreement with the Fundamental Principles of the International Red Cross and Red Crescent Movement (humanity, impartiality, neutrality, independence, voluntary service, unity, and universality) VMF aimed in particular at implementing the notion of equal right to health treatment, by reaching out to the most vulnerable drug users, by offering its services even in areas of high drug trafficking and drug use, and by avoiding wait-and-see policies that ultimately penalize those in the greatest need of help. In the words of VMF Founding President, Dr Massimo Barra: “As long as the addict is alive there is hope of improvement. When the addict dies hope dies with him”.

In its 30 plus years, the Foundation has grown from a small centre assisting around five persons a day to providing services to 800 drug users per day and more than 3,000 patients and their families a year. The main focus is to build trust with drug users, in the knowledge that therapies will not help unless they follow a process in which the drug user believes.

Dr Barra comments: “If we consider individuals in their different phases of life, we can realize that every individual is quite different from the next and that even differences can be found in the same individual. For this reason, treatment and dependence therapies have to be tailored towards the real and changing needs of a particular individual. Therapies have to be shaped for individual needs and not vice-versa....”.

The Villa Maraini is now recognized as the Italian Red Cross Agency on Drug Abuse and has become one of the world’s leading centres in substance abuse treatment and prevention, serving as a reference both within the Red Cross Red Crescent and externally. It serves as a safe centre for those in need, working to mitigate the stigma and potential public health consequences of the spread of transmissible diseases as well as offering drug rehabilitation programmes.

## 2. The basic problem: overdose on opioids

### 2.1 Addictive drugs: opioids

Opioid **agonists** (chemicals that produce a biological response) represent one of the most important classes of addictive drugs. The first opioids to be used by humans were the opiates (morphine and codeine) contained in the dried latex or juice of the seed pod of the opium poppy (*Papaver somniferum*). The opium poppy was domesticated during the Neolithic period in Central and Southern Europe. From there, the cultivation spread to the Middle East and then to the Far East over a period of several thousand years. It is very likely that the opium poppy was initially cultivated to obtain its seeds as a source food and for oil, and opium was used for medicinal and ritual purposes<sup>1</sup>. Contrary to what is commonly thought, there is limited evidence of recreational use of opium in the ancient world<sup>2</sup>.

It was only in the 16<sup>th</sup> century that a series of geographical and technological discoveries made it possible to smoke opium in pipes (first mixed with tobacco and then alone) and to concentrate its active principles in alcoholic extracts. The isolation of morphine (1804), the invention of the hypodermic syringe (1850s), and the synthesis of heroin (1874) set the stage for transforming opioid addiction into a global social and health problem<sup>3</sup>. The prevalence of opioid addiction surged and ebbed (with marked regional differences) during the twentieth century, but in the last decade it reached epidemic proportions. A recent report by the United Nations Office on Drug and Crime<sup>4</sup> indicates that in 2014 about 17 million people, between the ages of 15 and 64, used opium, morphine or heroin. When prescription opioid **agonists** are also considered, the prevalence of users rises to about 33 million.

### 2.2 Opioid abuse and the risk of overdose

The risk of “overdose” is probably the major problem linked to opioid abuse. The mortality rate of European opioid users is about five to ten times greater than their peers of the same age and gender, and overdose represents the most common cause of death<sup>5</sup>. These figures are compatible with the findings of other studies<sup>6,7</sup>. The actual number of deaths due to opioid overdoses is not easy to estimate. In 2014, according to UNODC<sup>4</sup>, there have been more than 200,000 drug-related deaths worldwide, and one third to one half of these deaths is attributed to opioid overdose. The World Health Organization estimates in fact that every year about 70,000 people die due to opioid overdose. The European Drug Report by the European Monitoring Centre for Drugs and Drug Addiction<sup>8</sup> (EMCDDA) estimates that opioid overdoses account for about 2.5 per cent of all deaths of Europeans aged 15–39, about 80 per cent of whom are male.

- 1 Merlin MD (2003) *Archaeological Evidence for the Tradition of Psychoactive Plant Use in the Old World*. *Economic Botany* 57:295-323.
- 2 Nencini P (2004) *Il fiore degli inferi: Papavero da oppio e mondo antico*. Franco Muzzio Editore: Roma.
- 3 Dormandy T (2012) *Opium: Reality's Dark Dream*. Yale University Press: New Haven and London.
- 4 UNODC (2016) *United Nations Office on Drugs and Crime, World Drug Report 2016*.
- 5 EMCDDA (2016) *European Drug Report 2016: Trends and Developments*. See: [www.emcdda.europa.eu/system/files/publications/2637/TDAT16001ENN.pdf](http://www.emcdda.europa.eu/system/files/publications/2637/TDAT16001ENN.pdf).
- 6 Hser YI, Hoffman V, Grella CE, Anglin MD (2001) A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry* 2001;58:503–8.
- 7 Hser et al (2015) Long-term course of opioid addiction. *Harv Rev Psychiatry*. 2015 Mar-Apr;23(2):76-89.
- 8 EMCDDA (2015) *European Drug Report 2015: Trends and Developments*. See: [www.emcdda.europa.eu/system/files/publications/974/TDAT15001ENN.pdf](http://www.emcdda.europa.eu/system/files/publications/974/TDAT15001ENN.pdf).

The data concerning the trend over time of opioid overdose in Europe require caution for a number of reasons, including systematic under-reporting in some countries and delays in the registration of cases. Countries with relatively robust reporting systems (e.g., Germany, Sweden, United Kingdom) report an increase in the number of overdoses in the past few years<sup>8</sup>. Another worrying trend is the increased number of overdoses due to opioids other than heroin.

Even more dramatic is the increase in the incidence of opioid overdose in the last two decades in the United States of America (USA), due to a steep increase in the abuse of both heroin and prescription opioids.

Only a small proportion of first-time opioid overdoses result in the death of the user<sup>9</sup>. The major reason for the relatively low mortality of the opioid overdose is the widespread use of the opioid **antagonist** naloxone. Indeed, the administration of naloxone in cases of opioid overdose represents one of the most important life-saving interventions in Accident & Emergency (A&E) departments. In a clinical context the treatment of the overdose is almost always successful. In contrast, the treatment of overdose outside the hospital setting is still unsatisfactory in too many cases<sup>10</sup>.

In 2015, the EMCDDA published a systematic review of the effectiveness of take-home naloxone in a series of studies involving 2,912 opioid users at risk of overdose in 19 communities. They were followed up for seven years. The review emphasized “that educational and training interventions complemented by take-home naloxone decrease overdose related mortality” and that “there is weaker, but consistent, evidence that similar interventions for opioid-dependent patients and their peers effectively improve knowledge, while forming positive attitudes to the correct use of naloxone and the management of witnessed overdoses”<sup>11</sup>.

Regrettably, the 2015 EMCDDA’s review did not acknowledge the pioneering role of the Italian Red Cross Villa Maraini Foundation (VMF) in the treatment of opioid overdoses in the context of the public street. Undoubtedly, this was due to limited circulation of VMF publications in English and to the fact that these publications were not primarily directed to the medical and scientific community. The main goal of this document is to redress this gap in the literature and to present evidence concerning the safety, the efficacy and the cost-effectiveness of naloxone administration by non-medical staff for the reduction of opioid overdose fatalities in the public street context.

<sup>9</sup> Darke S, Mattick RP, Degenhardt L (2003) The ratio of non-fatal to fatal heroin overdose. *Addiction*. 2003 Aug; 98(8):1169-71.

<sup>10</sup> WHO (2014) Community management of opioid overdose.

<sup>11</sup> EMCDDA (2015) Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone, *EMCDDA Papers, Publications Office of the European Union, Luxembourg*. See: [www.emcdda.europa.eu/publications/emcdda-papers/naloxone-effectiveness](http://www.emcdda.europa.eu/publications/emcdda-papers/naloxone-effectiveness).

<sup>12</sup> In particular, mu, kappa and delta **receptors**, distributed widely in the brain, spinal cord and digestive tract.

## 2.3 How overdose affects the body

Opioid **agonists** (such as morphine, heroin, codeine, oxycodone, methadone, fentanyl and its derivatives, etc.) as well as partial **agonists** (such as buprenorphine) stimulate opioid **receptors**<sup>12</sup> located at various levels of the brain and the body, thereby producing a number of central and peripheral effects. The most remarkable effects of opioid **agonists** include:

1. euphoria
2. **analgesia**
3. constipation
4. cough suppression
5. depression of the central nervous system (CNS)

Depression of the CNS results in relief of anxiety, sedation, sleepiness, and most important for the scope of this report, depression of the respiratory centres of the brain<sup>13</sup>. At high dosages, the depression of the CNS and in particular of the respiratory centres is so profound that they produce the classical signs of overdose:

1. extreme sleepiness or unconsciousness
2. pinpoint pupils not responding to light
3. slow, irregular, or absent breathing
4. **cyanosis** (especially around the lips and under the fingernails) due to **hypoxia**
5. **crackles**
6. lack of pulse

If the overdose is not treated rapidly with naloxone, death might ensue.

## 2.4 Risk factors for overdose

**Suicide tendency.** There is limited information about the association between suicide tendency and opioid overdose. A recent study found that suicide attempts (not involving heroin) were significantly more common among those who had taken unintentional overdoses compared with those who had never overdosed<sup>14</sup>. However, it should be mentioned that “intentional overdose” does not necessarily equate to “suicide”, in the sense of having the intention of causing one’s own death<sup>15</sup>. Indeed, it is unlikely for an addict to use her/his usual drug when attempting to commit suicide<sup>16</sup>. Very often, sizeable amounts of drug are found in the pockets of individuals who have died of overdose, suggesting that they were looking forward to outcomes other than death<sup>17</sup>. As noted by Barra and Lelli<sup>18</sup>, “for the heroin addict the overdose is always around the corner, it is part of the game, part of the risk and perhaps of the pleasure of drug taking [...] every time the addict injects something the exact content of which cannot be known for sure death is a possibility, the addict plays with death hoping to survive”<sup>19</sup>.

**Tolerance.** Repeated exposure to opioid **agonists** can produce tolerance to some of their effects. This leads the addict to increase the dose to continue to experience the “high”. Some effects of the opioids, however, undergo relatively little tolerance, as in the case of respiratory depression, which may result in overdose.

**Abstinence or sporadic use.** Tolerance to the CNS-depressant effects of opioid drugs is relatively modest (see above) but not absent. After discontinuation of the drug, tolerance slowly disappears. Thus, overdoses are frequent when the addict relapses after a period of abstinence (typically associated with detention or residential detoxification), even if the dose was the same as in the period preceding abstinence<sup>20,21,22</sup>. Also, sporadic users are at a greater risk of overdose relative to daily users<sup>23</sup>.

**Variable heroin content in “street heroin”.** While the concentration of the active principle in prescription opioids (e.g., methadone, fentanyl, oxycodone) is known, except in cases of adulteration, the concentration of heroin in “street heroin” is virtually unpredictable. An interesting forensic study by Risser and colleagues found, for example, that the concentration of heroin in street samples seized in Austria varied from 0.0 per cent to 47 per cent. Thus, heroin addicts are particularly exposed to the risk of unintentional overdose. In September 1995, a batch of unusually “pure” street heroin caused eight deaths over the course of a few days in Palermo (Sicily, Italy) and VMF led a taskforce charged

- 13 Pattinson KT (2008) Opioids and the control of respiration. *Br J Anaesth*. 2008 June; 100(6):747-58.
- 14 Brådvik L, Frank A, Hulenvik P, Medvedeo A, Berglund M. Heroin addicts reporting previous heroin overdoses also report suicide attempts. *Suicide Life Threat Behav*. 2007 Aug; 37(4):475-81
- 15 Neale J. (2000) Suicidal intent in non-fatal illicit drug overdose. *Addiction*. 2000 Jan; 95(1):85-93.
- 16 Vingoe L, Welch S, Farrell M, Strang J. (1999) Heroin overdose among a treatment sample of injecting drug misusers: accident or suicidal behavior? *J. Subst. Use*, 4 (1999), pp. 88–91.
- 17 Barra M. (1997) Droga dalla A alla Z, McGraw-Hill, Milano.
- 18 Barra M, Lelli V (2014) 30 years of Naloxone. *Heroin Addict RelatClinProbl*.
- 19 A similar point was made, from a psychoanalytic perspective, by Musatti (*Curare nevrotici con la propria autoanalisi* (1987), pp 143–150): “It is totally useless to explain to an addict that taking the drug [heroin] may lead to death. The addict is fully aware of that. In a certain sense, the addict sees the drug experience as a way to disappear, a different type of death: a sweet and liberating death. A death that would free the addict even from the desperate prison of drug addiction”.
- 20 Püschel K, Teschke F, Castrup U. (1993) Etiology of accidental/unexpected overdose in drug-induced deaths. *Forensic Sci Int*. 1993 Nov; 62(1-2):129-34.
- 21 Donoghoe MC (1999) Opioid overdose: an international perspective. *Addiction*. 1999 Nov; 94(11):1745-6.
- 22 Darke S, Hall W, Kaye S, Ross J, Duffou J. (2002) Hair morphine concentrations of fatal heroin overdose cases and living heroin users. *Addiction*. 2002 Aug; 97(8):977-84.
- 23 Brugal MT, Barrio G, De LF, Regidor E, Royuela L, Suelves JM. (2002) Factors associated with non-fatal heroin overdose: assessing the effect of frequency and route of heroin administration. *Addiction*. 2002 Mar; 97(3):319-27.

with dealing with this emergency. In the ensuing three months more than one hundred heroin overdoses were treated with naloxone, all of them successfully.

**Association with other substances.** The severity of the opioid overdose can be exacerbated by association with other CNS depressants, such as alcohol, benzodiazepine, and barbiturates<sup>24,25,26</sup>. Also, the association of heroin and cocaine is linked to increased frequency of fatalities. Heroin is often mixed with cocaine in a “speedball”, or taken after cocaine in order to counteract the stimulant effects of the latter. In this case the **pathogenesis** of the overdose is thought to depend on the discrepancy between the **hypoxia** produced by respiratory depression and increase in heart rate produced by cocaine. Furthermore, the psychostimulant effects of cocaine might mask the CNS-depressant effects of heroin and facilitate excessive heroin intake.

**Route of administration.** Not surprisingly, the risk of overdose is much greater after intravenous (i.v.) injection than with other routes of administration<sup>27</sup>.

**Physical and mental health.** Systemic diseases may increase the risk and the severity of opioid overdose. Chronic liver diseases such as hepatitis C and B are common in i.v. drug users. The resulting liver damage decreases heroin **metabolism**, thus prolonging its **half-life** and that of its active **metabolites**<sup>28</sup>. Also, infectious and tobacco-related lung diseases are common in i.v. users. Respiratory insufficiency combines with heroin-induced respiratory depression to produce severe **hypoxia**<sup>29</sup>. Among people with HIV, opioid overdose is a common cause of death not directly related to the infection, although the mechanism for this increased risk is not clear<sup>30</sup>.

**Age.** About one in two people who die of opioid overdose in Europe are aged 40 or over<sup>31</sup>. Yet this portion of the population represents only one fourth of the total population of opioid addicts, at least based on the age distribution of those seeking treatment<sup>32</sup>. This apparent increase in the risk of overdose in older addicts may depend not only on increased health problems but also on the physiological changes associated with normal ageing. It is also possible, as proposed previously by Barra<sup>33</sup>, that repeated exposure to the physical and psychological stressors associated with drug addiction progressively wears the addict’s body down. It has been shown, for example, that repeated non-fatal overdoses increase the lethality of subsequent ones<sup>34</sup>.

**VMF classification of risk.** Based on the points discussed above, VMF classifies heroin addicts in overdose in four categories of decreasing risk:

1. poly-drug users: more than one CNS-depressant drug (Benzodiazepine, alcohol, barbiturates) used in the same day, even if not at the same time
2. abstinent individuals who have just completed a detoxification programme, a period of detention, or a residential programme requiring abstinence
3. occasional drug users
4. drug users who have recently changed dealer

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## 3. Naloxone: a life-saving drug

Naloxone (Narcan®) is a competitive mu, kappa and delta opioid **receptors antagonist**. The concentration of naloxone is extensively reduced as it passes through the liver after oral administration resulting in a **bioavailability** of only two per cent<sup>35</sup>. Thus, this route of administration is not viable. Naloxone can be administered instead using routes other than oral: intravenous injection, injection under the tongue, injection through skin or into a muscle, spray into nose or throat. In selecting the route of administration four main factors must be taken into consideration:

1. clinical picture
2. peripheral vein accessibility
3. available formulation of the naloxone
4. setting of the intervention

When possible, the intravenous route is to be preferred, as it produces high brain concentrations of naloxone very rapidly. The onset of action is about one to two minutes and the effect lasts for one to four hours. Unfortunately, most addicts have very poor superficial veins and this route of administration is often impossible.

The under the tongue route of administration is almost as fast-acting as the intravenous one but it is not easy to implement (at least in the experience of the VMF), as the addict might abruptly close his/her mouth, resulting in injuries to both the addict and the rescuer. Naloxone is rapidly absorbed into the network of veins that lie underneath the mucous membranes in the mouth and transported through the facial veins into the systemic circulation.

The intramuscular route of administration is the most practical as it can be managed by laypersons with minimal training. Generally, one or two vials of 0.4 mg naloxone are sufficient to deal with moderate overdoses. The intramuscular injection is also recommended for the first intervention, eventually followed, if possible, by intravenous or under the tongue injection.

The recently introduced intranasal administration (nasal spray) of naloxone is certainly the most manageable by laypersons but it is often less than optimal because many addicts have a history of intranasal use of cocaine, heroin (or other opioids), or methamphetamine, which is associated with destruction, scarring, perforation, loss and death of tissue in the nose, nasal mucous membranes and tissues in the middle part of the throat (oropharynx).

The **half-life** of naloxone is approximately one hour, significantly shorter than that of many opioid **agonists** and therefore respiratory depression may recur as blood levels of naloxone fall. Naloxone has an excellent safety profile and adverse effects rarely occur (allergic reaction, fluid in the lungs, heart rhythm problems, seizures). Few, if any, of these potential side effects have been observed by VMF.

<sup>35</sup> Gibson CM, Pass SE. (2014) Enteral naloxone for the treatment of opioid-induced constipation in the medical intensive care unit. *J Crit Care.* 2014 Oct; 29(5):803-7.

## 4. Villa Maraini Foundation (VMF) overdose treatment programme

At the time of the establishment of VMF, naloxone was not yet available and the only therapeutic option for reversing the opioid overdose was nalorphine, a mixed opioid **agonist-antagonist**. At doses that exert significant antagonism against heroin, nalorphine also produces respiratory depression, and therefore should be administered only at relatively low doses and under strict medical supervision<sup>36,37,38</sup>. The introduction of naloxone, which does not possess **agonist** properties<sup>39,40</sup>, represented a sea change in the treatment of the opioid overdose. In particular, naloxone could be administered at high dosages and if necessary the treatment could be repeated several times with no danger to the patient.

### 4.1 The Street Unit

The Red Cross Red Crescent principles informing the activity of VMF made it impossible to accept that despite the availability of a life-saving medication, heroin addicts could still die of overdose in large numbers. The major obstacle to providing effective treatment in a timely manner is represented by the setting in which many overdoses take place. Indeed, heroin overdoses often occur in isolated, hidden, hard to reach locations, and often the addict is alone. Even when the addict is not alone, fatalities can occur in more than half of all cases, as the other addicts present on the scene are often unable to diagnose the event, are themselves incapacitated by the drug, or are reluctant to seek help for fear of arrest.

Hence, in 1992 the VMF set up its first Street Unit, with the aim of reaching drug addicts with no access to regular substance misuse services. At that time, naloxone was available only on medical prescription and its administration required the presence of a physician. Thus, the staff of the Street Unit initially included a physician in addition to psychologists, social workers (former drug users) and Red Cross volunteers. In 1994, as no major adverse events were registered in the first years of naloxone use, the Italian authorities, after a massive advocacy campaign conducted by VMF and other Civil Society Organizations, eliminated the need for prescription and classified naloxone as a life-saving medication, making it compulsory for every pharmacy to have at least one package of naloxone in stock. Despite this requirement, this is not the reality in all the pharmacies.

**Training social workers to manage overdose.** One of the defining aspects of the therapeutic strategy of VMF has always been the fight against the unfortunate stigma of addiction and the emphasis on the empowerment of addicts and former addicts in the therapeutic process. Thus, in 1994, the VMF began training former addicts as social workers to administer basic life support and naloxone for the treatment of opioid overdoses. In their new capacity as social workers, former addicts provide added value to the quality of team intervention,

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especially in the street context. They speak the same slang as drug users, are more trusted than professional staff, and have first-hand experience of all aspects of drug taking. Over the years, these social workers have played a crucial role in contacting drug users and enrolling them in the therapeutic programmes of the VMF.

### Training peers, partners, relatives, police officers and fire-fighters.

Any delay in providing first aid intervention in cases of heroin overdose increases the risk of death for the user. Even when the overdose takes place in the home environment and the addict is found by friends or relatives when still alive, the addict can still die while waiting for an ambulance or during transport to hospital. Thus, it is important that not only heroin addicts but also people who live or work with them, or may come in contact with them because of their profession (e.g., police officers and fire-fighters), receive basic training on how to manage an overdose and how to administer naloxone. Over the years the take-home naloxone programme of VMF has distributed 0.4 mg vials of naloxone to hundreds of individuals at high risk of heroin overdose. Furthermore, family members, partners, peers, police officers and fire-fighters have been trained to identify individuals at risk, to prevent the occurrence of overdose, to diagnose overdose, to assess its severity, and finally to deliver basic treatment. These training sessions also emphasize the dangers of intravenous injection, of using heroin obtained from unknown sources, of mixing heroin with other drugs or alcohol, and of using heroin after a drug free period and/or in isolated places or when alone.



## 4.2 VMF overdose treatment protocol

The Street Unit of VMF has developed a protocol of overdose treatment, to be used by both medical and non-medical staff. This protocol is the result of 25 years of experience in the treatment of overdoses in extremely difficult and potentially dangerous settings.

**Step 1.** The first step consists of a rapid initial assessment of the overdose scenario by the rescuer(s) and in the adoption of safety precautions to avoid injuries. The rescuer should look for visible signs of recent injection (blood, needle track marks), drug paraphernalia (syringes, needles, tourniquets, bags containing substances, etc.), and scarring of peripheral veins (indicating a long history of intravenous drug use).

**Step 2.** If naloxone is available, an intramuscular injection of 0.4 mg should be administered immediately. The patient can receive an additional 0.4 mg of naloxone in case of severe intoxication with unconsciousness, **cyanosis** and **crackles**. In life-threatening situations the injection should be performed through clothing to avoid any delay in the treatment.

**Step 3.** Call the emergency services.

**Step 4.** Cardiac and respiratory functions must be assessed and if necessary cardio-pulmonary resuscitation (even in the absence of cardiac arrest and especially when naloxone could not be administered) should be carried out according to standard Basic Life Support (BLS), Basic Life Support and Defibrillation (BLS-D) or Advanced Life Support (ALS) protocols.

**Step 5.** If after two minutes there is no response, 0.4 mg of naloxone should be administered again, possibly intravenously. The opportunity to attempt the intravenous injection should be evaluated based on the age of the patient. A long history of intravenous drug use (leading to **phlebitis, thrombosis** and scarring) makes it unlikely that peripheral venous access can be gained<sup>41,42,43</sup>. Thus, intravenous naloxone administration is usually performed in young individuals (aged 20 or younger). When the intravenous route is not viable the rescuer should consider the sub-lingual route, injecting naloxone into the mucosa of floor of the mouth above the **mylohyoid muscle**. In this case a long needle should be used to minimize the risk of injuries to either the rescuer or the patient (as sometimes the patient can abruptly close the mouth). The injection should be performed slowly and can be repeated at two-minute intervals until the patient recovers.

It is important to emphasize that the VMF naloxone programme is fully consistent with the WHO guidelines for the “Community management of opioid overdose”, although the programme began many years before the publication of these guidelines. These recommendations include:

- People likely to witness an opioid overdose should have access to naloxone and be instructed in its administration to enable them to use it for the emergency management of suspected opioid overdose. Naloxone is effective when delivered by intravenous, intramuscular, subcutaneous and intranasal routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting and local context.
- In suspected opioid overdose, first responders should focus on airway management, assisting ventilation and administering naloxone.
- After successful resuscitation following the administration of naloxone, the level of consciousness and breathing of the affected person should be closely observed until full recovery has been achieved.

**Avoiding the withdrawal syndrome.** When using naloxone to treat an overdose the rescuer should avoid the risk of producing the opposite consideration, that is, a withdrawal syndrome. The opioid withdrawal syndrome is not in itself a life-threatening condition but is extremely unpleasant. Symptoms and signs include: anxiety, irritability, restlessness, bone and joint aches, muscle cramps, tremors, nausea, vomiting, diarrhoea, profuse sweating, piloerection (goose bumps), runny nose, tears, uncontrollable sneezing, high heart rate, high blood pressure, yawning and pupil dilation. This intensely disagreeable physical and mental state can lead to the refusal of further assistance (with the risk that opioid overdose could recur) and to using heroin again. Since the **half-life** of heroin is much longer than that of naloxone, injecting heroin to overcome the effects of naloxone may produce an overdose that is more difficult to treat than the first one. Furthermore, inducing a withdrawal syndrome might be dangerous for the rescuer(s) as it is associated with aggressive behaviour targeting in the first place the persons involved in the intervention, who are perceived as a threat to the patient. Thus, naloxone administration should be **titrated**, or measured continuously and the dose adjusted, so as to re-establish vital functions without provoking withdrawal symptoms.

41 M Woodburn KR, Murie JA (1996) Vascular complications of injecting drug misuse. *Br J Surg.* 1996 Oct; 83(10):1329-34. Review.

42 Van Beek I, Dwyer R, Malcolm A (2001) Cocaine injecting: the sharp end of drug-related harm! *Drug Alcohol Rev.*, 20 – 2001, pp. 333-342.

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## 4.3 Effectiveness of the VMF naloxone programme

From 25 March 1992 to 31 December 2017 the Street Unit of VMF performed more than one million interventions, including:

- 21,200 contacts with individuals with substance use disorders
- 340,737 condoms were provided
- 1,351,948 sterile syringes were distributed
- 704,023 used syringes were collected
- More than 2,500 opioid overdoses were treated (305 in 1992–1996; 687 in 1997–2001; 398 in 2002–2006; 522 in 2007–2011; 323 in 2012–2017).

Note that in the first years of activity not all interventions were recorded.

It must be emphasized that the primary aim of VMF's activities, consistent with its Red Cross affiliation, is saving life. Thus, given the extremely difficult and potentially dangerous circumstances under which the VMF Street Unit operates and the constraints in term of available staff, the collection of data concerning its activities has taken a back seat relative to the need to provide life-saving interventions in a timely manner.

However, in the period January 2015 to October 2016 an effort was made to collect data aimed at assessing the efficacy of the service according to the criteria established by the Regional Health Council of Lazio Region (Italy). The most relevant data thus collected are illustrated in Tables 1–3 and Figure 1. It is important to point out that 90 heroin overdoses were treated, all of them successfully. Eighteen individuals were treated for more than one overdose on different dates.

Table 1 provides basic information concerning the demographics of the sample.

**Table 1 Demographic data (md = missing data)**

<b>Number of overdoses</b>	90		
<b>Number of individuals</b>	72		
<b>Sex</b>		<b>Nationality</b>	
Female (%)	10 (13.9%)	Italians (%)	70 (97.2%)
Male (%)	62 (86.1%)	Others (%)	2 (2.8%)
<b>Age</b>		<b>Age of first heroin use (md=9)</b>	
Years (average)	39.8	Years (average)	19.8
<b>Education (md=38)</b>		<b>Years of heroin use (md=5)</b>	
5-7 years (%)	1 (2.9%)	> 10 (%)	48 (71.6%)
8-12 (%)	22 (64.7%)	6-10 (%)	11 (16.4%)
≥ 13 (%)	11 (32.4%)	1-5 (%)	7 (10.4%)
		< 1 (%)	1 (1.5%)
<b>Marital status (md=6)</b>		<b>Frequency of heroin use (md=6)</b>	
Single (%)	43 (65.2%)	> 1/day (%)	26 (39.4%)
Married (%)	6 (9.1%)	1/day (%)	11 (16.7%)
Partner (%)	7 (10.6%)	> 1-6/week (%)	16 (24.2%)
Separated/divorced (%)	9 (13.6%)	< 1/week (%)	13 (19.7%)
Widowed (%)	1 (1.5%)		

Table 2 reports on the circumstances of the overdose while Table 3 shows the treatment programme in which the patients were enrolled at the time.

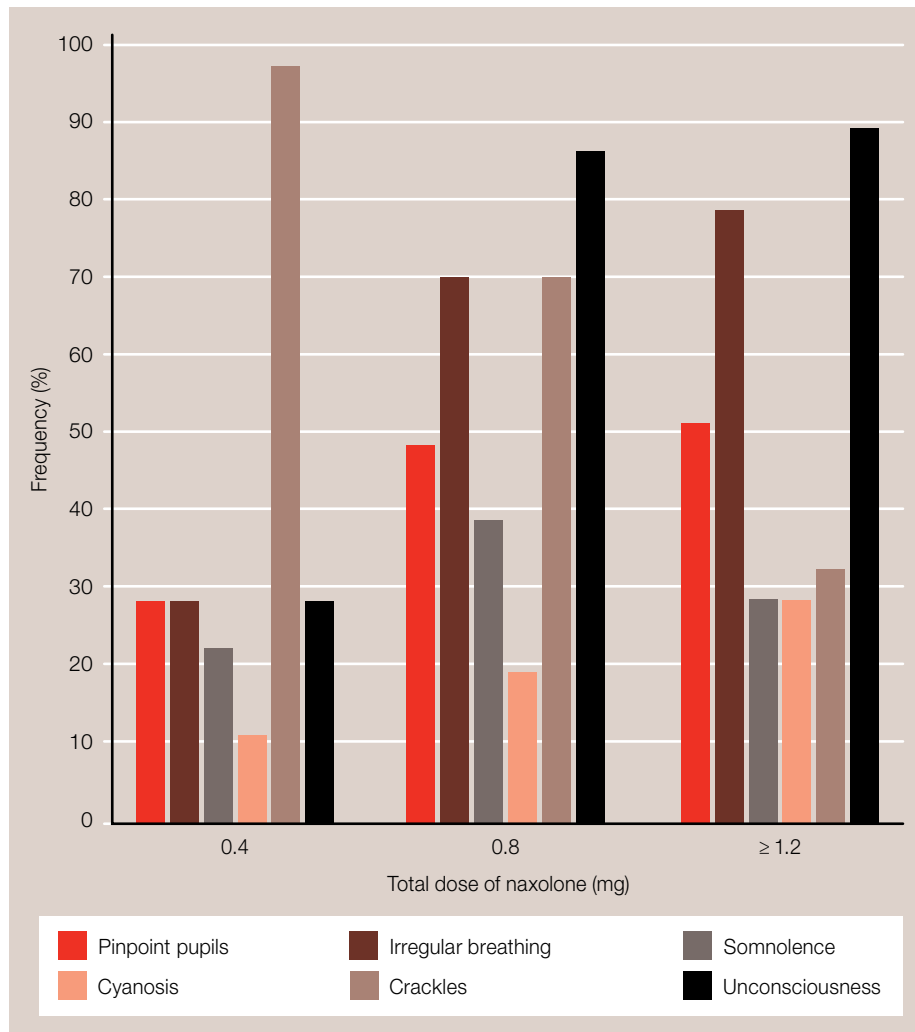
**Table 2 Circumstances of the overdose (md = missing data)**

<b>Physical setting</b> (md=2)		<b>Withdrawal syndrome</b> (md=8)	
Street (%)	66 (75%)	Yes (%)	5 (6.1%)
Park (%)	22 (22.7%)	No (%)	77 (93.9%)
Other (%)	2 (2.3%)		
<b>Social setting</b>		<b>Recent release from prison</b> (md=10)	
Alone (%)	26 (28.9%)	< 3 days (%)	2 (2.5%)
In company (%)	64 (71.1%)	3-7 days (%)	0 (0.0%)
		> 7 days (%)	13 (16.25%)
		None (%)	65 (81.25%)
<b>Increase in dose</b> (md=6)		<b>Days from last heroin injection</b> (md=11)	
Yes (%)	7 (8.3%)	< 3 days (%)	53 (67.09%)
No (%)	77 (91.7%)	3-7 days (%)	10 (12.66%)
		> 7 days (%)	16 (20.25%)
<b>Change in dealer</b> (md=10)		<b>Poly-drug use</b> (md=7)	
Yes (%)	6 (7.5%)	Benzodiazepine (%)	19 (22.6%)
No (%)	74 (92.5%)	Cocaine (%)	9 (10.7%)
		Alcohol (%)	4 (4.7%)
		Street Methadone (%)	3 (3.6%)
		Cocaine + Benzodiazepine (%)	2 (2.4%)
		Cocaine + Alcohol (%)	2 (2.4%)
		Alcohol + Benzodiazepine (%)	1 (1.2%)
		Amphetamine + Benzodiazepine (%)	1 (1.2%)
		None (%)	42 (50%)

**Table 3 Treatment programme in which the patients were enrolled**

<b>Structure/organization</b> (md=4)			
Methadone Public Service			30 (34.9%)
Therapeutic community			5 (5.8%)
None			51 (59.3%)
<b>Therapeutic programme</b> (md=7)		<b>Take-home naloxone</b> (md=16)	
Methadone decreasing doses	11 (39.3%)	Yes	16 (21.6%)
Methadone maintenance	14 (50%)	No	58 (78.4%)
Psychosocial	3 (10.7%)		

Figure 1 below shows the total dose of naloxone administered as a function of the clinical picture.

**Figure 1 Total dose of naloxone administered**

## 4.4 Cost-effectiveness of the VMF naloxone programme

The VMF Street Unit provides an alternative to hospitalization for the treatment of heroin overdoses in the street context. Thus, it is important to compare the cost-effectiveness of the two options. However, the usual approaches to the evaluation of the cost-effectiveness of therapeutic programmes had some limitations, particularly because the function of the therapy in this programme is to save a life. As a matter of principle, we felt that there is not a market price for the human life. Other mathematical modelling tools failed to consider the whole picture, particularly ignoring the setting or environment of the interventions.

To overcome these limitations, we therefore used a methodology derived from the concept of economical evaluation, i.e. “the comparative analysis of alternative courses of action in terms of both their costs and consequences”<sup>44</sup>. One possibility is to calculate the costs of a naloxone intervention (the opportunity cost) versus the gains (the benefit): this is based on a cost function coherent with the theory of marginal analysis, i.e. looking at additional benefits of an activity in comparison to the additional costs incurred by that activity<sup>45,46</sup>. However, public health authority

<sup>44</sup> Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. (2015) *Methods for the Economic Evaluation of Health Care Programmes 2015, fourth edition*. Oxford University Press.

<sup>45</sup> Doran C. (2007) *Economic Evaluation of Interventions for Illicit Opioid Dependence: a review of evidence*. University of Queensland Australia Background Document Prepared For Third Meeting Of Technical Development Group (TdG) For The Who “Guidelines For Psychosocially Assisted Pharmacotherapy Of Opioid Dependence” 17-21 September 2007 Geneva, Switzerland.

<sup>46</sup> Pedersen KM. (2012) A New Paradigm for Health Economics? *Nordic Journal of Health Economics Online* ISSN: 1892-9710 University of Southern Denmark.

and public opinion need a measure of the allocation of health resources in terms of its ability to improve the quality of life at three levels: individual, social and medical. The first level concerns the would-be patient; the second concerns the general health status of the community; the third level concerns the epidemiological status of the population. The most appropriate methodology to achieve these goals in our case is to compare the cost of the intervention implemented by the VMF Street Unit with the fee charged by the A&E department of a hospital.

The hospital costs are easy to calculate because they can be derived from the mechanism of reimbursement adopted by the Italian National Health System, which like most other European health systems employs the Diagnosis-Related Group (DRG) classification of hospital cases<sup>47</sup>. Opioid overdoses are classified as DRG 454 or DRG 455 (with and without complication, respectively)<sup>48</sup>. The cost for each admission is 1,704 euros for DRG 455 and 2,593 euros for DRG 454. The DRG includes a maximum stay of 21 hospital days but the reimbursement remains the same independent of the actual length of stay.

The calculation of the costs for the VMF Street Unit is more complex, as the service contract with the Regional Health Agency covers the entire activity of the Street Unit and not only the interventions for overdose. The actual financial worth of the intervention should be calculated by taking into account the financial value of human and material resources used, the saving in terms of health care, and the social impact of reducing the damage of the opioid-related deaths. Additional factors to be taken into consideration are represented by the reduction of social damage (e.g., family and other personal relationships) and the reduced spreading of infectious diseases (e.g., HIV, Hepatitis C etc.). However, the estimate of these gains would be based on a series of theoretical assumptions about which there is no consensus. At present, the overall service provided by VMF Street Unit includes (in addition to the treatment of street overdoses): prevention, information, training in safety measures, alert system, deterrence of smugglers/pushers, control of the territory, first aid and other types of therapeutic intervention. The cost of the Street Unit is 83,125 euros for 180 days of services equivalent to ten calendar months. The overdose interventions represent a fraction of the total. A calculation of the financial cost of the service for 90 interventions produced the following figures, in euros:

• Labour	14,774.40
• Medical supplies and technical resources	2,101.57
• VMF's resources	13,116.98

<sup>47</sup> Busse R, Geissler A, Quentin W, Wiley M. (2011) edited by Diagnosis-Related Groups in Europe Moving towards transparency, efficiency and quality in hospitals, *Open University Press McGraw-Hill Education - Copyright © World Health Organization 2011 on behalf of the European Observatory on Health Systems and Policies.*

<sup>48</sup> GU (2013) *Gazzetta Ufficiale del 28-1-2013 Supplemento ordinario n. 8 Serie generale - n.23.*

The table below summarizes the comparison between the financial value of the 90 naloxone interventions carried out by two VMF Street Units (located near Termini Station and in the area of Tor Bella Monaca, respectively) and the cost of 90 interventions in the absence of the Street Units (that is, 90 potential hospital admissions for DRG 454 or DRG 455). For this comparison two scenarios were chosen. In the best-case scenario all interventions are without complications (DRG 455). In the worst-case scenario all interventions are with complications (DRG 454). The savings for the NHS vary from 123,367.05 euros (best-case scenario) to 203,377.05 euros (worst-case scenario).

Item	Overdoses	Financial costs to the NHS	Financial cost of the VMF	Saving (Euros)
<b>Worst-case scenario</b> (all DRG 454)	90	233,370.00	29,992.95	203,377.05
<b>Best-case scenario</b> (all DRG 455)	90	153,360.00	29,992.95	123,367.05

## 5. Conclusion

Too many addicts still die because of an overdose in the street. In most cases these deaths could be prevented by the timely administration of naloxone. Villa Maraini Foundation has pioneered the training of former addicts for the diagnosis of overdose and its treatment with injectable naloxone in difficult street contexts. The saving of these lives not only fulfils the institutional aims of an organization affiliated to the International Red Cross and Red Crescent Movement, but it also meets more concrete societal needs. Indeed, the data reported here clearly show the cost-effectiveness of naloxone programmes run by the VMF Street Unit relative to a comparable service provided by the health care system. It is important to emphasize the range of services provided from the VMF Street Units including first aid to the drop-outs and people with abuse problems, prevention, information, support to the fight against drug smugglers and aid to territorial control. These services are not included in the financial cost to the NHS expressed in DRG, as the calculation of these costs lies outside the scope of this paper.

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# The Fundamental Principles of the International Red Cross and Red Crescent Movement

**Humanity** The International Red Cross and Red Crescent Movement, born of a desire to bring assistance without discrimination to the wounded on the battlefield, endeavours, in its international and national capacity, to prevent and alleviate human suffering wherever it may be found. Its purpose is to protect life and health and to ensure respect for the human being. It promotes mutual understanding, friendship, cooperation and lasting peace among all peoples.

**Impartiality** It makes no discrimination as to nationality, race, religious beliefs, class or political opinions. It endeavours to relieve the suffering of individuals, being guided solely by their needs, and to give priority to the most urgent cases of distress.

**Neutrality** In order to enjoy the confidence of all, the Movement may not take sides in hostilities or engage at any time in controversies of a political, racial, religious or ideological nature.

**Independence** The Movement is independent. The National Societies, while auxiliaries in the humanitarian services of their governments and subject to the laws of their respective countries, must always maintain their autonomy so that they may be able at all times to act in accordance with the principles of the Movement.

**Voluntary service** It is a voluntary relief movement not prompted in any manner by desire for gain.

**Unity** There can be only one Red Cross or Red Crescent Society in any one country. It must be open to all. It must carry on its humanitarian work throughout its territory.

**Universality** The International Red Cross and Red Crescent Movement, in which all societies have equal status and share equal responsibilities and duties in helping each other, is worldwide.

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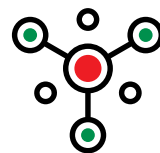
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